

## Review Article



## Nanoparticles: Therapeutic Benefits for Diabetes Mellitus by Oral Delivery

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### ABSTRACT

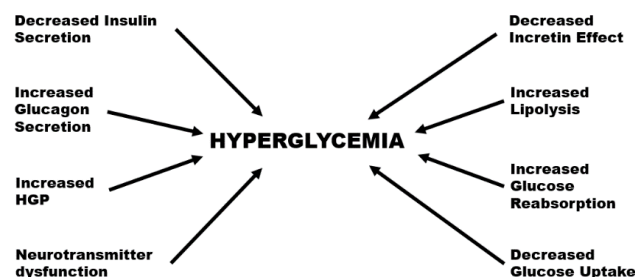
Nanotechnology is of great scientific interest in development studies as they are effectively a bridge between bulk materials and atomic or molecular structures. It is used as carrier for delivering molecules such as drugs, proteins and genes, hence have gained tremendous importance in biology and medicine. Several drugs are successfully encapsulated in nanocarriers to improve its bioavailability, bioactivity and control delivery and effectiveness in curing disease. Such carriers have a high intracellular uptake due to their small size and easy mobility. These dosage forms can also be altered to deliver drug in triggered release pattern at the site of action and protect them from enzymatic degradation in the adverse gastrointestinal (GI) environment. They are so-called smart drug delivery systems designed to respond to certain stimuli like pH, temperature, redox potential, enzymes, light and ultrasound. Also, the effect of stimuli of glucose responsive drug release system is beneficial for management of diabetes mellitus. This review gives a brief overview of nanocarriers and its types, for the management and treatment of diabetes mellitus.

**Keywords:** Diabetes mellitus, Oral delivery, Nanoparticles, Targeted delivery, Stimuli-sensitive.

### INTRODUCTION

Diabetes mellitus (DM) is a major socio-economic burden with serious health consequences affecting body's ability to use food as an energy source. It is a heterogeneous disorder characterized by multiple defects in the pancreatic beta cell, liver, and peripheral tissue such as skeletal muscles and adipose tissue, and by chronic elevation of blood glucose i.e. hyperglycaemia over a prolonged period<sup>1</sup>. The growing incidence of DM led to increase the number of affected patients worldwide. According to the recent data of International Diabetes Federation (IDF), about 425 million adults had diabetes for 2017, and the number will rise to 700 million in 2045<sup>2</sup>. Diabetes mellitus occurs either when the pancreas does not produce enough insulin or when body cannot effectively use the insulin it produces<sup>3,4</sup>. The goal of mimicking natural fluctuations in insulin levels throughout the day is prime requirement. Typical therapeutic treatment includes insulin and analogues, incretin hormones (GLP-1 and GIP), peptide YY and amylin<sup>5</sup>. Diabetes mellitus is known to be associated with degradation of pancreatic beta cells, insulin resistance and hyperglycaemia<sup>6</sup>. Although about 25% of DM patients are already diagnosed with micro-vascular complications indicating that they have had the disease for more than 5 years at the time of diagnosis. The development of DM often be the causative factor of increased risks of many micro- and macro-vascular complications such as stroke, retinopathy, neuropathy, nephropathy, coronary artery disease, hypertension and peripheral vascular disease<sup>7,8</sup>. The type-1 DM caused mainly due to genetic factor whereas "ominous octet" lists the causes of hyperglycaemia proposed for eight pathophysiological mechanisms underlying type-2 DM occur in isolation or in

combination as mentioned in fig.1. These include reduced insulin secretion from pancreatic  $\beta$ -cells, elevated glucagon secretion from pancreatic  $\alpha$  cells, increased production of glucose in liver, neurotransmitter dysfunction and insulin resistance in the brain, enhanced lipolysis, increased renal glucose reabsorption, reduced incretin effect in the small intestine and impaired or diminished glucose uptake in peripheral tissues such as skeletal muscle, liver and adipose tissue<sup>9</sup>.



**Figure 1:** Eight pathophysiological mechanisms underlying T2DM

The endmost aim behind treatment is to lower and maintain glycosylated haemoglobin level below 7% to minimize the risks of complications associated with disease<sup>10</sup>. Diabetes mellitus if in case left untreated, prolonged hyperglycaemia leads to complications whereas, insulin overtreatment may cause hypoglycaemia, leads to seizures, unconsciousness or death. So it is important to monitor the glucose level in blood of diabetic patient<sup>11</sup>. Some classes of anti-diabetic possess poor solubility because of which incomplete absorption from gastrointestinal tract and hence low bioavailability<sup>12</sup>. The hindrances in effective oral delivery of proteinaceous molecules involves low stability, poor

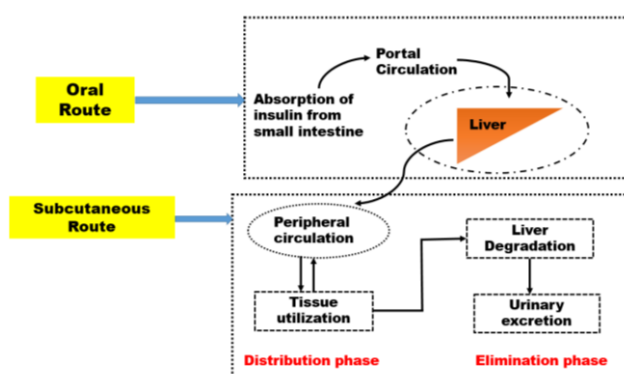


absorption and lack of lipophilicity resulting in low permeation through intestinal and interstitial tissues and rapid inactivation or degradation by gastrointestinal (GI) enzymes, bioavailability and therapeutic efficacy of dosages are affected<sup>13</sup>. Since nanoparticles have a large surface area compared to microspheres, drug incorporated in nanoparticles possess several interesting and unique properties such as improved pharmacokinetic and pharmacodynamics properties, increased dissolution velocity, increased mucoadhesion properties and increased saturation velocity<sup>14, 15</sup>. There is need for the development of a novel formulation that will improve drug's bioavailability, escalate absorption rates, enables site-specific drug delivery which can be achieved by means of nanotechnology.

Nanotechnology is the science of materials and devices whose structures and constituents gives novel and considerably altered physical, chemical and biological phenomenon due to their nanoscale size, featuring between  $10^{-9}$ m and  $10^{-7}$ m. Nanoparticles are developed to deliver both small-molecule and large macro-molecular (DNA, RNA and proteins) therapeutics, as well as to diagnose and monitor the progression of disease. Drugs that exhibit poor stability in the gastric fluid, low solubility and mucus barrier can prevent drug penetration and absorption, these factors may alter drug's bioavailability. Developing nano-formulations to encapsulate and protect drugs and release them in a controlled manner to surpass these limitations. The polymers, such as chitosan, alginate, etc. play an important role in the release pattern and stability of drug delivery through nanocarriers. Another approach of delivery system as nanocarriers that release cargo in terms of responsive to stimuli by the trigger generating biomolecule like glucose. At the physiological pH, this biomolecule responds to certain substances such as glucose oxidase enzyme, lectins-concanavalin A and also small synthetic molecule- phenyl boronic acid, when they are incorporated in nanocarriers for trigger effect<sup>16, 17</sup>.

#### NECESSITIES AND CHALLENGES OF ORAL DRUG DELIVERY

The oral administration of peptide is patient compliant, as it mimics the natural physiological fate of insulin<sup>18</sup>. It takes the advantage of a portal-hepatic delivery, shown in fig.2, where portal circulation is involved, insulin is targeted to the liver, and inhibits hepatic glucose production, hence a better glucose homeostasis is observed<sup>19</sup>. Whereas in Subcutaneous route, drug bypasses the portal circulation and reaches directly to peripheral circulation led to occasional hypoglycaemia and peripheral hyperinsulinemia. Although there are certain advantages, several limitations persist while delivering protein and peptide by oral route<sup>20</sup>.



**Figure 2:** Schematic diagram illustrating the absorption distribution and elimination of insulin following oral or subcutaneous administration

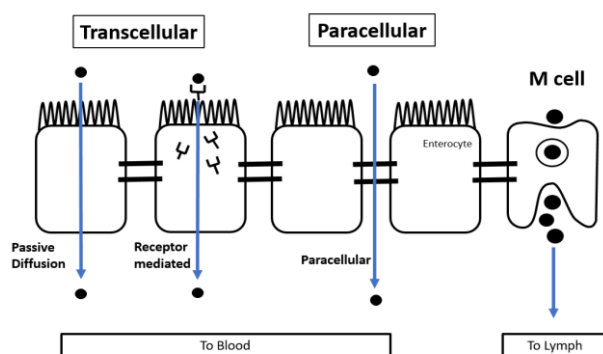
Inactivation of the hormone by enzymatic digestion in stomach and intestine as well as poor permeability of the intestinal epithelium, owing to its high molecular weight and lack of lipophilicity and rapid pre-systemic degradation are the factors for poor oral bioavailability<sup>21</sup>.

Several other routes such as buccal, nasal, ocular, vaginal and rectal had been tried for the insulin delivery and enhancing its bioavailability<sup>22, 23, 24</sup>. Delivery of insulin via the ocular route was tested in animal models in combination with different absorption enhancers. Vaginal and rectal routes was investigated, their absorption rate and bioavailability showed poor results due to the thick mucosal layers in these tissues. Nasal delivery was evaluated and concluded that highly active mucociliary clearance in nose hindered drug absorption resulting in poor bioavailability. Oral and sublingual insulin administration provides better results in comparison to the above. Oral route is considered to be the most feasible and convenient method of drug administration to improve compliance among diabetic patients<sup>25</sup>. Subcutaneous injection remains the preferred approach for insulin delivery for treating diabetic patients, but this route does not follow glucose homeostasis as observed in the normal subjects<sup>21</sup>. The oral drug delivery is known for its convenience, cost effectiveness and patient compliance, but for some drugs when exposed to strong gastric acid and pre-systemic enzymatic degradation, result in poor systemic exposure. Hence, it is a challenge to achieve adequate and consistent bioavailability levels for orally-administered drugs. Oral delivery of drugs using nanotechnology is beneficial in delivery of poorly water-soluble drugs, transcytosis of drugs across the tight intestinal barrier, targeting of drugs to specific part of gastrointestinal tract and in intracellular and transcellular delivery of bulky macromolecules<sup>26</sup>.

There are number of barriers in the GI tract giving rise to challenges for oral drug delivery, which must be overcome, so that drug reaches systemic circulation and gets absorbed. The pH environment of stomach, macromolecular size of protein and enzymatic degradation may serve as drug delivery barriers<sup>27</sup>. The pH environments in GI tract may cause pH-induced oxidation,

deamidation or hydrolysis of protein therapeutics, leading to its loss of activity. The proteases, nucleases, and lipases secreted for enzymatic reaction so that biological molecules get digested prior to absorption. The intestinal mucosal barrier can be categorized as extrinsic and intrinsic barriers. Extrinsic barrier consists of microenvironment overlying the mucus layer of epithelial cells. Whereas, intrinsic barrier consists of epithelial cell monolayer behaves as the major restrictive barrier to passive diffusion of material from lumen to the lamina propria<sup>28</sup>.

There are several pathways for molecules to cross the epithelial cell membrane, given in fig. 3, which include transcellular (transport through the cell), paracellular (transport between adjacent cells), and transcytosis transport pathways. Because of the size and charge of biologics, most of them are restricted to the transcytosis pathway, an active transport pathway that relies on receptors to bind and guide material in endosomes through the cell without entering a degradation pathway<sup>28, 29</sup>.



**Figure 3:** Transport pathways of intestinal cells

The barriers associated with oral drug delivery can be overcome by developing nanoparticles that protects from harsh pH and enzymes, increased mucoadhesion, increased retention in gastrointestinal tract and release of drug in a controlled manner. Also, nanoparticles helps to improve stability of the drugs in gastro intestinal environment<sup>30</sup>. However, colloidal instability generally leads to nanoparticle aggregation or flocculation, therefore chemical stability is very important, especially for the nanocarriers involving specific targeting ligands, which ensures the binding of nanocarriers to a specific receptor and delivery of therapeutic agents<sup>31</sup>.

## TARGETED DELIVERY AND PRINCIPLES OF NANOPARTICLES

Targeted delivery of drug is a selective drug delivery to specific physiological sites, organs, tissues, or cells where a drug's pharmacological activities are required, but if drug reaches the sites other than therapeutic sites may lead to toxicity. Active targeting focuses on specific interactions such as antigen-antibody and ligand receptor binding, at target site that efficiently delivers the drug at specific target. Magnetic field and temperature are

physical signals act as external stimuli for active targeting at target sites. Whereas passive targeting is a method in which physical and chemical properties of carrier systems increase target/nontarget ratio of quantity of drug delivered by adjusting these properties to physiological and the histological characteristics of target and nontarget tissues, organs, and cells<sup>32</sup>.

Nanoparticles are highly permeable, thus drug with high potency has high risk of toxicity when they are received by unwanted target sites. Targeting the drug molecule to a proper and required address site reduces the side-effects to a higher extreme than covering drug in well-designed carrier package which lowers the risk up to some extent. Targeting is referred to as steering drug particles exclusively to disease site. Therefore, ideal requirement of this carrier system is to deliver the drug molecules at a particular tissue site and into specific cells. Targeting involves the evasion of immune system, and crossing of physical, chemical and metabolic barriers<sup>33</sup>.

## TYPES OF NANOPARTICLES

The efficacy of drug is determined by delivery of nanocarriers at targeted site. Failure of drug to reach the target site leads to failure in drug therapy, as the presence of barriers at various body compartments causes hindrance to drug delivery<sup>34</sup>. Nanoparticles are designed such that the disintegrative chemical and mechanical conditions, and extremes of pH are encountered in gut. After oral administration, nanoparticles can enter the bloodstream, where they may cause pathological changes in liver and kidney tissues, necessitating rigid pharmacokinetic and toxicological studies of nanoparticles<sup>35</sup>. The large molecular weight and hydrophilic nature of molecule lowers its efficiency for its diffusion across the GI tract epithelial cells, which shows low permeability across mucosal surfaces and biological membrane. These factors contribute to the low bioavailability issue that prevents efficient and reliable oral drug delivery<sup>36, 37</sup>.

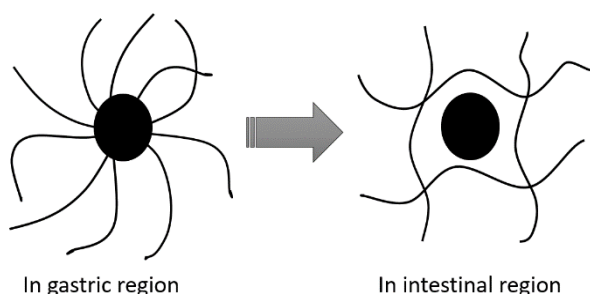
Following are the types of nanoparticles studied for efficient oral drug delivery:

### 1. Polymeric nanoparticles:

Polymeric nanoparticles are developed from biocompatible and biodegradable polymers has been extensively studied for developing therapeutic carriers to encapsulate hydrophilic and/or hydrophobic small drug molecules, as well proteins and nucleic acid macromolecules. The active drug molecules are dissolved, encapsulated or entrapped in a polymeric matrix depending on the method of preparation of nanoparticles. This type of nanoparticle is a promising system for drug encapsulation and protection from pH variations and enzymatic attacks, allowing drug release in systemic region. Polymer used to formulate nanoparticles are chitosan/ tripolyphosphate, alginate/ chitosan, poly(lactide-co-glycolic acid) (PLGA) and poly(isobutylcyanoacrylate) which are currently involved

in the encapsulation of insulin<sup>38-41</sup>. The physicochemical parameters like surface charge play a critical role in nanoparticle uptake by intestinal barrier, hence modification in surface charge of nanoparticles are needed. The negatively charged sodium dodecyl sulfate (SDS) nanoparticles showed better and improved internalization compared to classical polyvinylalcohol nanoparticles (+PVA NPs) and chitosan-coated nanoparticles determined in the Caco-2 model<sup>42</sup>. The smaller particle size (submicron) of nanoparticle are absorbed and transferred through the intestinal mucosa, consequently this enhances drug bioavailability, stability and protects from enzyme degradation. Modification of nanoparticle surface with poly(ethylene glycol) enables the nanoparticles to penetrate mucus barrier<sup>28</sup>. Repaglinide nanocrystals were developed using high pressure homogenization technique, polymers such as PEG 4000, Poloxamer 188 and PVA were used, Taguchi design applied to optimize type of polymer, % polymer concentration, number of cycles, and HPH pressure in the formulation<sup>43</sup>. The carbopol was studied for its mucoadhesion activity since this retains the drug in gastrointestinal tract for a prolonged period of time and offers sustainable release<sup>44, 45</sup>.

## 2. pH-Responsive nanoparticle



**Figure 4:** pH responsive polymeric network

The organs, tissues, and subcellular compartments in the body, their pathophysiological states are characterized by their different pH levels and gradients. When exposed to these variant pH levels, the polymeric nanoparticles respond with physicochemical changes to their material structure and surface characteristics, includes swelling, dissociating or surface charge switching, in a manner that favours drug release at the target site over surrounding tissues<sup>46</sup>. The mechanism of stimuli responsive hydrogels is that shift in pH causes change in the charge on polymer chains leading to swelling and drug release, as shown in fig.4. Example poly(acrylic acid), Guar gum succinate, Kappa-carrageenan/poly(vinyl alcohol) etc.<sup>47</sup>. The pH-responsive based systems have been exploited in order to protect drugs and enhance its bioavailability by surpassing the problem of low efficacy of drug is due to low pH of gastric medium in stomach and various digestive enzymes in gastrointestinal tract which degrade drug. These drug carriers are stable under acidic conditions of stomach, also can rapidly release cargoes under neutral pH in intestine, which beneficial in

targeting drug to the intestine or protecting drug from gastric medium.

The pH responsive nanoparticles were used as carrier system to enhance the bioavailability of monomeric insulin analogue, aspart-insulin, prepared by ionic gelation method using chitosan and poly (gamma-glutamic acid)<sup>21</sup>. These nanoparticles enhanced the oral absorption of insulin, also facilitating glucose uptake by insulin-responsive tissue which resulted in lowering of postprandial hyperglycaemia<sup>48</sup>.

The  $\gamma$ PGA-EGTA nanoparticles act as Calcium specific depleting agent, leads to inhibition of the activity of intestinal protease enzymes and enhancement of the paracellular permeability by stimulating endocytosis of apical junction complex (AJC) components of Caco-2 cell monolayers function as reversible opening of AJCs.  $\gamma$ PGA-EGTA develops a significant and prolonged hypoglycemic effect, by prevention of enzymatic degradation of insulin and modulation of transepithelial resistance resulting in enhancement of paracellular permeability of insulin. The EGTA-conjugated carrier has a good efficacy as it increases the bioavailability of orally administered insulin<sup>49</sup>.

The nanoparticles were developed using Ionotropic gelation method by incorporating polymers such as chitosan and xanthan gum, sodium tripolyphosphate as a cross-linking agent, in which the hydrophilic polypeptide insulin was entrapped successfully. The synergistic hypoglycemic activity were observed by the addition of xanthan gum possessing hypoglycemic property<sup>50</sup>. The utilization of mucoadhesive formulations such as alginate/silica nanoparticles for oral delivery were developed for cell-penetrating peptides (CPP)-insulin conjugates. At low acidic pH of stomach fluid these alginate/silica nanoparticles will shrink and hinder the release of insulin-CPP complexes, while at higher pH of intestine these alginate NPs will undergo swelling and will subsequently release these insulin-CPP complexes for efficient translocation across the epithelium were observed<sup>51</sup>. Hydrogels which are sensitive to specific environmental changes and show responses by changing their shape or volume when exposed to certain conditions are regarded as stimuli sensitive hydrogels. These are sensitive to (i) physical stimuli such as light, pressure, temperature, electric field, magnetic field, ultrasound; (ii) chemical stimuli such as pH, redox, ionic strength, CO<sub>2</sub>, glucose, and (iii) biological stimuli such as enzymes, antigens, glutathione, and DNA<sup>47</sup>.

The feasibility of combining bovine insulin and exendin-4 in nanoparticles that composed of chitosan and poly gamma glutamic acid resulted in enhancement of intestinal permeation and increase in the bioavailability of combination therapy<sup>52</sup>.

## 3. Lipid nanoparticles

Solid lipid nanoparticles (SLN) have promising effect for improving the oral bioavailability of protein. They are



primarily made of lipids that remain solid state at room temperature or body temperature, are beneficial for oral protein delivery<sup>53</sup>. Nanoparticles offers advantages such as high biocompatibility, feasibility of production on large industrial scale and ability of lipid matrix to protect proteins from degradation by GI acids and enzymes<sup>54, 55</sup>. Hydrophobic nature of SLN generally accounts for low peptide entrapment efficiency (EE%). Therefore, incorporating a hydrophilic viscosity-enhancing agent (VA) within SLN cores, developed viscosity enhanced nanocarriers (VEN), resulted improvement in peptide EE%. The agents such as propylene glycol (PG), polyethylene glycol (PEG) 400 and PEG 600, were tested with human insulin serving as a model peptide drug and the effects of VA were both concentration- and type-dependent<sup>56</sup>. SLNs were developed to incorporate low water-soluble drug- repaglinide, in which lipid phase consisted of stearic acid and glyceryl mono stearate (GMS) and phosphatidylcholin, tween80, pluronic F127, poly vinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) as surfactant/stabilizer. The Tween80-based SLNs resulted in smallest size, phosphatidylcholin-based SLNs indicated most prolonged drug release time and the highest loading capacity<sup>57</sup>.

#### 4. Metal nanoparticles

Zinc oxide and silver nanoparticles act as potent antidiabetic agents, also these were evaluated for their antidiabetic activity, showed a significant reduced blood glucose, higher serum insulin, higher glucokinase activity higher expression level of insulin, insulin receptor, GLUT-2 and glucokinase genes in diabetic rats treated with zinc oxide, silver nanoparticles and insulin<sup>58</sup>. The microwave-assisted method was applied for synthesization of ZnO nanoparticles in the presence of fruit extract *Vaccinium arctostaphylos* L. However, a decrease in crystallite size was observed for the biologically synthesized ZnO compared to chemically synthesized sample. The existence of organic moieties over biologically synthesized ZnO NPs was approved using characterizing methods. ZnONPs act as insulin secretagogue and also it does not possess risk of hypoglycaemia in an individual<sup>59</sup>.

#### 5. Glucose responsive nanocarriers

The development of smart stimuli responsive drug delivery strategies for diabetes is promising approach, as the need to vary dosage based on real-time disease state of patient. However the ultimate goal of this development would be to create a “Fully Synthetic Pancreas”, which is an abiotic construct that can sense elevations in blood glucose and respond with a metered dose of insulin, and/or glucagon, for closed-loop therapy<sup>60, 61</sup>. The progress in generation of insulin variants with tunable pharmacokinetics, remains a need to improve the fidelity of glycemic control to avoid both acute and long-term complications that arise in diabetes management<sup>62</sup>. Although polymeric nanoparticles possess attractive features of enhancing the insulin delivery through oral route, but their sustained release mechanism is

independent of the physiological blood sugar concentration. Therefore, the glucose responsive nanocarriers plays an important role in non-invasive glucose monitoring drug release system, which is one of the stimuli responsive carrier system that perform triggered based drug release. Glucose responsive can be achieved by developing the delivery system consisting of glucose-sensing elements such as enzyme glucose oxidase, lectins like concanavalin-A (Con-A) and the synthetic molecule such as phenyl boronic acid (PBA) that can bind glucose<sup>63, 64</sup>.

##### a) Glucose oxidase based delivery

The glucose-sensitive drug delivery systems based on glucose oxidase (GOD), exhibits highly promising applications in diabetes therapy in recent years. The self-regulated drug release systems monitor drug release with glucose concentration present in blood plasma<sup>65</sup>. GOD is a homodimer composed of two identical 80 kDa subunits and two non-covalently bound flavin adenine dinucleotide complexes. When GOD is incorporated with pH-responsive polymer materials, the pH change of micro environment is observed due to enzymatic oxidation of glucose to gluconic acid catalyzed by GOD in presence of glucose. The change in pH induces swelling or shrinking of GOD-incorporated carriers or the acidic biodegradation of GOD-containing polymer matrices, resulting in drug release. The glucose-sensitive drug delivery systems based on GOD are expected to be a typical candidate for smart platforms for potential applications in diabetes therapy. Also, the GOD-immobilized platforms applications are studied for its self-assembly layer-by-layer (LbL) films and polymer vesicles, cross-linking hydrogels and microgels, hybrid mesoporous silica nanoparticles, and micro devices fabricated with insulin reservoirs<sup>66</sup>. A new biomimetic insulin delivery strategy has been developed using glucose-responsive polymer nanovesicle. The enzymatic conversion of glucose into gluconic acid in the aqueous core of vesicles reduces local pH, resulting in hydrolysis of mildly acidic-degradable components of assembled polymers and dissociation of vesicles, therefore facilitating the release of encapsulated insulin. According to the in-vivo studies demonstrated for this nanovesicle resulted in highly biocompatible and effective in regulating blood glucose levels for a long period of time<sup>67</sup>.

##### b) Glucose-binding protein based drug delivery

Glucose-responsive materials have also been developed using lectins, a family of carbohydrate-binding proteins, concanavalin A (ConA) a tetravalent binding protein, as natural receptor-based glucose-sensing elements. The binding specificity of ConA for carbohydrates has used protein as a tetravalent cross-linker in the preparation of polymeric hydrogels, where both naturally occurring polysaccharides and synthetic polymers containing saccharide-like substituents have been explored in this approach<sup>68, 69</sup>. Concanavalin-A (Con A) and glucose oxidase (GOD) act as building blocks to be assembled into



{Con A/GOD}<sub>n</sub> LbL films mainly because the driving force of assembly was specific lectin-glycoenzyme recognition between them. The mechanism of stimuli-responsive properties of films toward probes mainly attributed to electrostatic interactions between films and probe. The construction of a pH stimuli-responsive enzyme-immobilized biointerface and intelligent bioelectrocatalysis of glucose is based on lectin-glycoenzyme biospecific LbL assembly, which has its potential application in designing new kinds of stimuli-responsive biosensors and bioelectronics devices. Based on specific biological interaction between lectin Con A and glycoenzyme GOD, {Con A/GOD}<sub>n</sub> LbL films were successfully assembled on various solid surfaces and GOD immobilized on the electrode surface. The films exhibit pH-dependent stimuli-responsive on-off properties toward different charged probes such as Fc(COOH)<sub>2</sub>, because of stabilized films prepared by unique lectin-sugar rather than electrostatic interaction, but the net charge of films could be easily tuned by solution pH. Also, electrostatic interaction between films and probe plays a key role in deciding the stimuli-responsive on-off behavior of system. Moreover, Fc(COOH)<sub>2</sub> not only acts as electroactive probe, also as the mediator for enzymatic electrocatalytic reactions. The {Con A/GOD}<sub>n</sub> films can be used to switch electrocatalysis oxidation of glucose catalyzed by GOD in films by altering environmental pH<sup>70</sup>. A new type of fluorescent ligand for FRET-based assays shown to improve the sensitivity of assay by improving accuracy of continuous glucose monitoring devices based on competitive binding sensing approach. This ligand is rationally designed to present a core trimannose structure and a donor fluorophore in close proximity to one another. This design decreases the distance between FRET donor and FRET acceptors on ConA to maximize FRET efficiency upon binding of the ligand to ConA<sup>71</sup>.

### c) Synthetic boronic acid based delivery

Boronic acids has been widely investigated for their potential use as glucose sensors in glucose responsive drug delivery systems. The complex formed between glucose and phenylboronic acid drives the swelling of hydrogels and consequently insulin release, eg. poly(acrylamide)-co-(3-acrylamidophenylboronic acid)<sup>72</sup>. The Phenyl boronic acid and its derivatives exhibit higher affinities with cis-diol compounds such as glucose to form stable glucose-PBA complex at neutral or alkaline pH, through reversible boronate formation, establishing the PBA-functionalized materials with promising applications in the self-regulated drug delivery system<sup>73</sup>. When glucose is added, the increase of hydrophilicity of PBA and polymer-containing carriers provides the swelling or disassembling of drug delivery vehicles, resulting in great glucose-sensitivity, hence endowing glucose-triggered drug release<sup>74</sup>. Oral delivery of insulin using a composite hydrogel system containing insulin-loaded glucose-responsive nanocarriers have multi-responsive properties, that has favorable equilibrium swelling behaviour between acidic and neutral pH environments

due to the protonation or deprotonation of carboxyl groups in acrylic monomers, the affinity recognition between phenylboronic acid (PBA) groups and glucose molecules and epithelial cell-targeting of folic acid (FA)<sup>75</sup>. This insulin-loaded composite hydrogel system exhibited relative lower cytotoxicity and excellent stability against protein solution which were proved by insulin release behaviour evaluation and hypoglycemic effect on diabetic Sprague Dawley (SD) rats. The further encapsulating this system into a three-dimensional (3D) HA hydrogel system enhances the oral bioavailability of insulin, also to overcome multiple barriers and providing multi-protection for insulin during the transport process. HA hydrogel systems containing insulin-loaded nanocarriers have a potential application in diabetes treatment via oral ingestion<sup>19</sup>.

**Table 1:** Summary of types of nanoparticle associated in the delivery of antidiabetic drugs

Sr. No.	Nanoparticles	Application
1	Polymeric nanoparticles	Used to encapsulate hydrophilic and/or hydrophobic drug molecules <sup>78</sup>
2	pH-Responsive nanoparticle	Beneficial in targeting drug to the intestine or protecting the drug from gastric medium <sup>47</sup>
3	Lipid nanoparticles	Benefits in enhancing physical stability, protection and controlled release <sup>79</sup>
4	Metal nanoparticles	ZnO and silver nanoparticles shown to have synergistic antidiabetic effect <sup>58</sup>
5	Glucose responsive nanoparticles	Being stimuli responsive carrier, its used as non-invasive glucose monitoring triggered based drug release <sup>63</sup>
a).	Glucose oxidase based delivery	As glucose levels increased, GOD embedded microgels swells in diameter over 1.6 times, promoting accelerated release of the encapsulated insulin. Hence, prolong normoglycemia <sup>65, 80</sup>
b).	Glucose-binding protein based delivery	The presence of free glucose seizes the specific binding sites of ConA-polymer complex, leading to its dissociation and release of cargo material <sup>81, 82</sup>
c).	Synthetic boronic acid based delivery	Glucose-responsiveness in this system arises from a disruption in cross-linking as free glucose competes with polymer i.e. PVA for binding to the PBA-containing polymer <sup>83, 84</sup>

The delivery systems were also developed by covalent bonding of phenyl boronic acid (PBA) and chitosan by direct reductive N-alkylation of chitosan with 4-formylphenylboronic acid (4-FPBA) which were assessed by FTIR, ToF-SIMS, SEM, DSC and glucose adsorption sensitivity measurements. The degree to which PBA was bonded to chitosan was related to 4-FPBA load used in



the reaction. Glucose adsorption sensitivity to PBA-bonded chitosan was directly related to the amount of PBA functionality within conjugates and physical nature of the matrices, like porous or crystalline. The crystalline nature of conjugates was confirmed by DSC, where exothermic event related to the melting of bonded PBA moiety, occurred at 338°C<sup>76</sup>. Interactions between cyclic diols and boronic acids, anchored to polymeric delivery systems results in swelling of delivery system, releasing the drug. The 4-formylphenylboronic acid conjugated chitosan was formulated into insulin containing nanoparticles via polyelectrolyte complexation. Changes in size of the nanoparticles and release of insulin were type of sugar- and concentration-dependent. High concentration of diols resulted in a sustained release of insulin due to crosslink formation with boronic acid moieties within the nanoparticles. The formulation has potential to be developed into a self-regulated insulin delivery system for the treatment of diabetes<sup>77</sup>.

## CONCLUSION

Nanoparticles are multiparticulate delivery systems designed to obtain prolonged or controlled drug delivery and to improve bioavailability as well as stability. This delivery system can also be advantageous as for limiting fluctuations within therapeutic range, reducing side effects, protecting drugs from degradation, decreasing dosing frequency and improving patient compliance and convenience. As it is stated in recent reports on oral delivery systems, it is obvious to have focus on polymeric nanoparticle drug delivery systems. Currently there are several different polymeric nanoparticles approaches being studied to overcome the barriers of intestine. However, these multifunctional nanomedicines which can enhance insulin absorption by transcellular or paracellular pathway and prolong gastrointestinal retention are responsible for improving bioavailability. It is believed that it will reach the goal of successful oral formulation due to development of such nanoparticles. Thus, nanotechnology has the immense potential to impact significantly on treatment of many diseases by enhancing therapeutic bioavailability, that are currently limited to parenteral administration.

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