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Review

Recent progress in polymeric non-invasive insulin delivery

Farzaneh Sabbagh [a], Ida Idayu Muhamad [b], Razieh Niazmand [c], Pritam Kumar Dikshit [d], Beom Soo Kim [a,*]

[a] Department of Chemical Engineering, Chungbuk National University, Cheongju, Chungbuk 28644, Republic of Korea
[b] Universiti Teknologi Malaysia, Department of Chemical Engineering, 81310, Johor, Malaysia
[c] Department of Food Chemistry, Research Institute of Food Science and Technology, Mashhad, Iran
[d] Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Guntur 522 502, Andhra Pradesh, India

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ABSTRACT

The design of carriers for insulin delivery has recently attracted major research attentions in the biomedical field. In general, the release of drug from polymers is driven via a variety of polymers. Several mechanisms such as matrix release, leaching of drug, swelling, and diffusion are usually adopted for the release of drug through polymers. Insulin is one of the most predominant therapeutic drugs for the treatment of both diabetes mellitus; type-I (insulin-dependent) and type II (insulin-independent). Currently, insulin is administered subcutaneously, which makes the patient feel discomfort, pain, hyperinsulinemia, allergic responses, lipodystrophy surrounding the injection area, and occurrence of miscarried glycemic control. Therefore, significant research interest has been focused on designing and developing new insulin delivery technologies to control blood glucose levels and time, which can enhance the patient compliance simultaneously through alternative routes as non-invasive insulin delivery. The aim of this review is to emphasize various non-invasive insulin delivery mechanisms including oral, transdermal, rectal, vaginal, ocular, and nasal. In addition, this review highlights different smart stimuli-responsive insulin delivery systems including glucose, pH, enzymes, near-infrared, ultrasound, magnetic and electric fields, and the application of various polymers as insulin carriers. Finally, the advantages, limitations, and the effect of each non-invasive route on insulin delivery are discussed in detail.

1. Introduction

Insulin, the most used protein drug for the treatment of diabetes mellitus patients in clinical practice, has long been considered a powerful medicine. It is also of predominant interest for oral drug delivery candidates. It is a 51 amino acid polypeptide discovered by Banting and Best in 1922 [1]. In 1923, Banting and Best were awarded the John McLeod Nobel Prize in the field of medicine [2]. The year 2021 was marked as 100 years since the discovery of insulin. As pancreas is the major organ involved in insulin secretion, Minkowski and von Mering started using the pancreas of dogs to study the various symptoms of diabetes as early as 1889. Minkowski's key findings corroborated that the pancreas secretes substances that can influence carbohydrate metabolism [3], including glucose oxidation, glucose production, and lipid metabolism, to name a few. During 1960–1970, many developments in the understanding of glucose homeostasis and insulin were implemented. Over the next years, the pharmacokinetics studies of insulin injection were performed [4].

Insulin is secreted in pancreas by β-cells of islets of Langerhans and plays an important role as a regulator, transportation, and storage of glucose within the body. This is the major anabolic hormone that regulates the carbohydrate and fat metabolism for energy production [5]. Glucose transporters in various organs such as muscle, fat tissues, and liver are functioned by the action of insulin. Conversely, glucose transporter activity in the above-mentioned organs and tissues is affected by insulin deficiency, leading to hyperglycaemia. Hyperglycaemia in the metabolic pathways and related disorders cause severe destruction to various functions of our body, especially blood vessels and nervous system. Besides, excess insulin in the body causes hypoglycaemia, resistance, and other undesirable side effects [6].

Current approaches to insulin rehabilitation rely mainly on substitution therapy, where subcutaneous delivery of exogenous insulin is replaced to mimic insulin secretion as like normal pancreas as possible. Although the satisfaction of insulin injection is already acknowledging,

* Corresponding author.
E-mail address: bskim@chungbuk.ac.kr (B.S. Kim).

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only around 20% of reported insulin injected through subcutaneously touches the liver (main site of action conferring to normal physiology) [7].

Many recovery options are currently in use, including replacement, repair with natural or synthetic alternatives, and regeneration when parts or more of tissues and organs die. Extracorporeal therapy, which pumps blood by a polymeric membrane exchange system, is the first alternative for diseased or damaged organs [8]. Hydrogels can be used as tissue engineering scaffolds because they have wide pores that support living cells. They can be engineered to dissolve or decay over time, releasing growth factors and allowing living cells to infiltrate and proliferate [9]. One major advantage of using hydrogels as tissue engineering matrices is their structural simplicity. In this process, cellular membrane receptor peptide ligands can be covalently incorporated to facilitate adhesion, proliferation, and development within the hydrogel matrix. Another advantage of using hydrogels is to protect drugs from aqueous environments. It behaves like a gel at body temperature and can be implanted into humans due to its biocompatibility nature [9].

The aim of the present review is to evaluate the latest improvements in diabetic disease control through non-invasive routes. Recent innovations in insulin delivery are described by highlighting the advantages and limitations of each route. Each non-invasive route includes many delivery methods focused on key methodological approaches and current applications that may facilitate improved treatment of diabetes patient. Some smart drug carriers are used to control blood glucose readings and time. Smart carriers for oral delivery of insulin include alginate, polyethylene glycol (PEG), salecan-based hydrogels, polyacrylic acid (PAA), and liposomes. Smart carriers for transdermal delivery of insulin contain microgels, pectins, microspheres, and hydrogels. Smart carriers applied for nasal delivery are starch and chitosan. Gel foam and micro-hydrogels are used as smart carriers for ocular delivery of insulin. Pluronic F-127 gel and chitosan are useful for rectal delivery of insulin. For vaginal delivery, microspheres and noisome are used for insulin delivery. Each method is described in detail.

2. Hydrogels as carrier for insulin delivery

Hydrogels are crosslinked hydrophilic polymer networks with a three-dimensional structure. Physical and chemical interactions create a compact and porous structure of the hydrogel, which holds enormous amounts of water. Hydrogels can accommodate a water content of 30–90 wt%. The water holding capability of hydrogel primarily depends upon the nature of the material or polymer used during synthesis [10]. Hydrogels are also recommended as good insulin delivery system controllers due to their excellent permeability to hydrophilic agents and their swelling properties [11]. Polymers are generally classified according to their origin into two main types: synthetic polymers and natural polymers. Both substances affect the transport of insulin across biological membranes [12]. Biomaterials produced from natural polymers have increased great attention for various applications due to their biodegradability and biocompatibility. Various natural polymers such as chitosan, cellulose, carrageenan, alginates, and starch can be reformed by chemical modifications to reveal certain functional and/or physical properties [13]. Recently, researchers have considered natural polymer-based hydrogels as the good candidate for wide range of applications including microencapsulation, drug delivery, and tissue engineering [14].

The polysaccharide-based hydrogels have many intrinsic benefits such as biocompatibility, biodegradability, and non-toxicity. The biocompatibility can be used to transport numerous drugs such as insulin [15]. Hydrogels can be used by insertions or implants and can be administered internally orally, subcutaneously, or intra-muscularly. Therefore, hydrogels can preserve appropriate levels of insulin in the bloodstream, shelter insulin from enzymatic degradation, and indirectly increase patient compliance [7].

Insulin delivery is the process of administering insulin to attain a therapeutic consequence in humans or animals. Smart polymeric carriers are settled for insulin delivery. Smart carriers are fabricated from materials that are responsive to physical (pH, temperature, or magnetic field), chemical (organic molecules, specific agents, or chemical agents), mechanical (pressure or mechanical stress), or biochemical (growth factors, protein, ligands, enzymes, or substrates) signals [16,17]. These transporters allow insulin to be delivered at an accurate time and a proper dosage in response to the stimulus only. For instance, the polymeric chains of the transporter expand with the increase in temperature, thus permitting insulin to diffuse out and be released from the carrier matrix [10]. Fig. 1 shows the most common micro/nano systems used for insulin drug delivery. In specific situations of the route in the body, insulin is released from the matrix.

3. Different types of stimuli-responsive insulin delivery systems

The use of stimuli-responsive polymeric carriers (Fig. 2) capable of releasing encapsulated insulin in response to changes in environmental stimuli or external activation could create a less invasive or non-invasive system for smart delivery of insulin from the reservoir in the body. Encapsulation of insulin in these stimuli-responsive vehicles may eliminate the need to improve patient safety, frequent subcutaneous injections, and compliance. The stimuli-responsive insulin delivery systems are discussed below.

3.1. pH-responsive insulin release

The pH value of the gastrointestinal tract rapidly rises from highly acidic (pH 1.0–3.0) in the stomach to pH 6.0–6.5 in the duodenum and to neutral or slightly alkaline (pH 7.0–7.5) along the jejunum and ileum [18]. pH-sensitive polymers appear to be suitable candidates for this purpose as they exhibit structural transitions when the pH of the environment fluctuates, thereby altering the solubility of the polymer and inducing swelling of the hydrogel. The pH-responsive carrier is stable and can protect the encapsulated therapeutic protein from the acidic conditions of the gastric environment and provides controlled release of the cargo at neutral pH when it reaches the small intestine [18]. This system releases insulin in a controlled manner according to the blood glucose level [19]. pH-responsive carriers such as alginate/κ- carrageenan composite hydrogel beads have been used for insulin delivery systems [20].

3.2. Enzyme-responsive insulin release

The design of materials with macroscopic properties is altered by the selective catalysis of enzymes. This type of sensitivity is unique because the enzyme is highly selective for reactivity, operates under mild conditions in vivo, and is an essential component of many biological pathways. Enzyme-responsive substances usually consist of an enzyme-sensitive substrate and another component that controls or directs interactions that lead to macroscopic transitions [21]. To convey enzyme sensitivity to a material, the incorporation of functional groups needs to react under enzymatic conditions. The most used glucose-sensitive moiety, glucose oxidase, can enzymatically convert glucose to gluconic acid in a biological environment. Glucose oxidation by glucose oxidase is usually accompanied by local O_2 consumption and rapid production of H_2O_2, which inactivates glucose oxidase [18].

3.3. Ultrasound-responsive insulin release

Ultrasound-responsive substances can deliver genes/drugs to target tissues and sonication causes genes/drugs to be released at specific sites. Insulin-loaded nanocapsules were embedded in chitosan microgels [22]. Insulin encapsulated in nanocapsules can diffuse passively from the nanoparticles but remain trapped by the microgel. After sonication, the

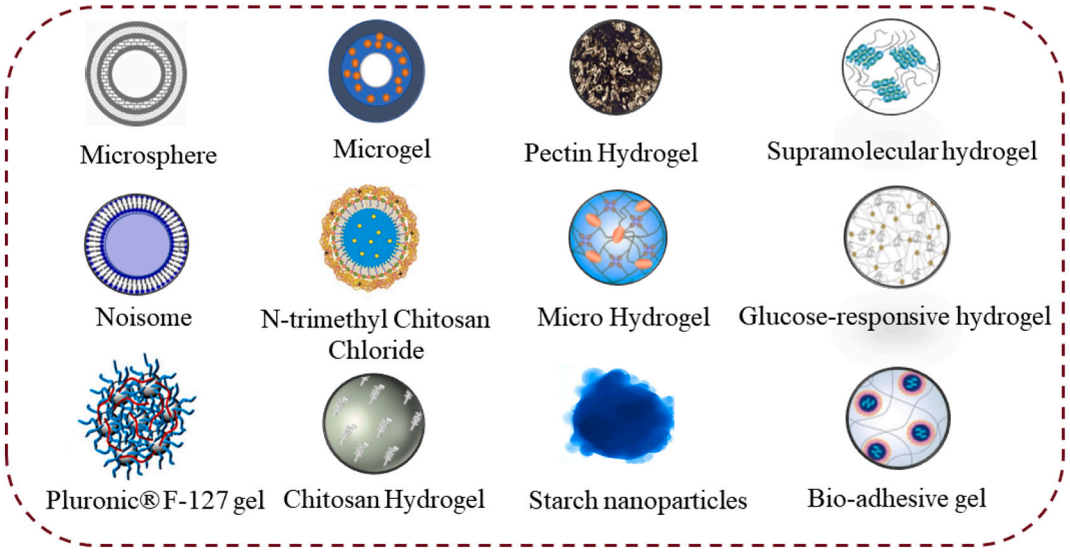

Fig. 1. The most common micro/nano systems used for insulin drug delivery. All these formulations have in common high specific surface area, small size, and high drug loading capacity.

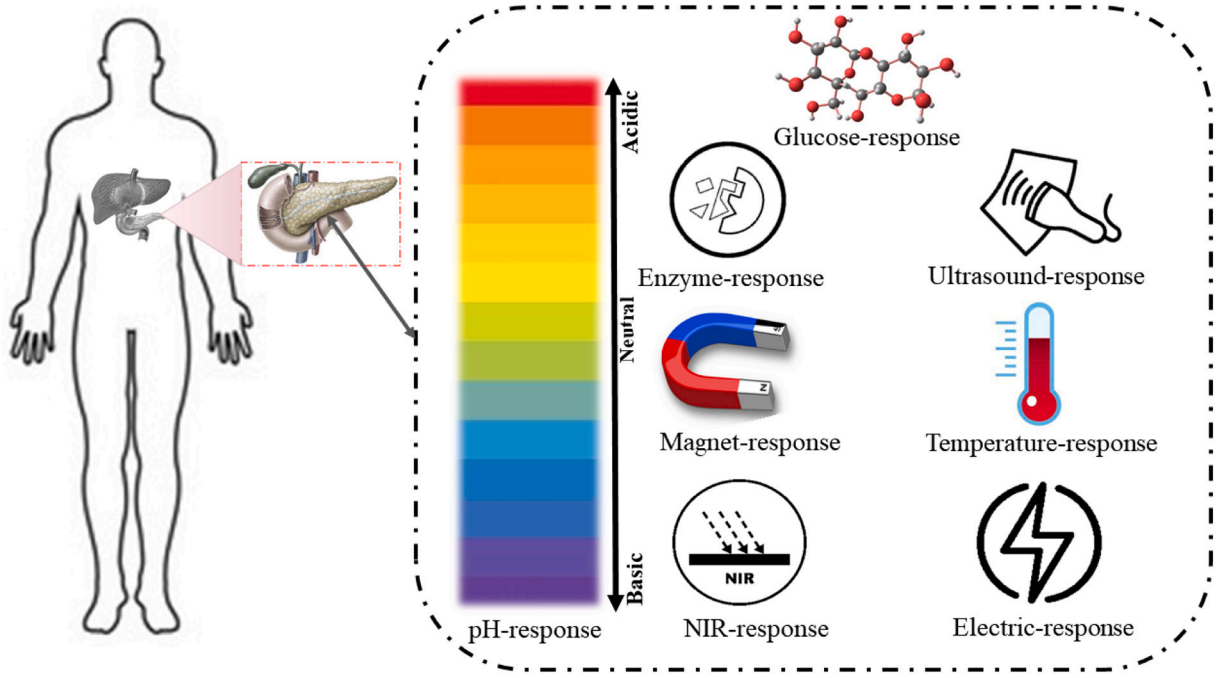

Fig. 2. Different types of stimuli used for insulin delivery.

insulin stored in the microgel can be rapidly released to control blood glucose levels. Commonly used polymer-based materials that respond to ultrasound include polymer-coated bubbles/emulsions (nanodroplets, microbubbles, nanoemulsions, and nanobubbles), polymer vesicles/micelles, and polymer hydrogels [23]. Poly(ethylene oxide)-*block*-poly [2-(diethylamino) ethyl methacrylate-*stat*-2-tetrahydrofuranyloxy) ethyl methacrylate] [PEO-b-P(DEA-stat-TMA)] is an example of ultrasound-responsive polymers that have been used in insulin delivery systems [23].

3.4. Glucose-responsive insulin release

Closed-loop-based smart insulin delivery, which can secrete insulin by mimicking β-cells in the pancreas in response to hyperglycaemia, is receiving increasing attention [22]. Typically, these closed-loop delivery systems consist of a glucose monitoring module and a glucose-induced insulin release module. One notable example is an electromechanical insulin pump consisting of a continuous glucose sensor and an external insulin infusion pump. Insulin infusion rates can be adjusted based on blood glucose level signals from glucose sensors in these wireless, portable, and wearable systems. Conversely, synthetic smart insulin delivery systems have been extensively studied to provide closed-loop delivery through formulation and material design [24]. These chemically closed-loop systems, usually based on glucose-responsive substances, can detect increases in blood glucose levels and respond to the release of certain amounts of insulin to control blood glucose [18]. 3-Acrylamidophenylboronic acid is an example of a glucose-responsive polymer for insulin delivery [25].

3.5. Temperature-responsive insulin release

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The temperature changes are relatively easy to control as well as easily adaptable in vivo and in vitro [26]. One of the unique characteristics of temperature-responsive polymers is the presence of a critical solution temperature. The critical solution temperature is the temperature at which the polymer and the solution (or other polymer) intermittently change with the composition of the phase [27]. The triblock copolymer of poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG) is an example of a temperature-responsive polymer used in insulin delivery systems [28].

3.6. Near-infrared (NIR)-responsive insulin delivery

An interesting strategy for controlled subcutaneous insulin delivery is based on a NIR-activated device consisting of a drug reservoir covered with an impermeable ethyl cellulose membrane containing gold nanoparticles [18]. Under the influence of NIR radiation, the gold nanoparticles are heated, resulting in the reversible collapse of the interconnected polymer nanoparticle network. By modulating the irradiation, a reproducible, repeatable, and customized method of insulin dose was created according to the needs of diabetic rats after subcutaneous injection [29]. Reduced graphene oxide (rGO) was introduced as a NIR-responsive material. Poly(ethylene glycol) dimethacrylate-based hydrogels containing rGO are an example of NIR-responsive polymer used in insulin delivery systems [30].

3.7. Electrical-responsive insulin delivery

Electrical potential has also been used as a trigger to activate insulin release [31]. When the potential pH of the hydrogel medium is positive or negative, the chitosan/layered double hydroxide shifts, resulting in faster insulin release. By tuning the electrical signal, different release rates can be achieved under physiological conditions. The rate of insulin release is regulated by the addition of various anions due to their interaction with ionic sites. The ability of insulin to bind to the surface is strongly influenced by external potential stimuli and pH [32]. Electro-responsive PAA and polymethacrylic acid hydrogels are examples of electrical-responsive polymers used in insulin delivery systems [32].

3.8. Magnet-responsive insulin delivery

Magnetic fields can be used to target and increase the residence time of magnetically responsive particles to improve delivery efficiency upon oral administration. An external magnetic field can localize magnetite-containing insulin carriers to the intestinal region, in which state the amount of insulin can be significantly increased, resulting in improved hypoglycemic effects [18]. Poly(ethyleneimine)/Fe_3O_4 is an example of magnetic nanoparticle used in insulin delivery systems [33].

4. Comparison of invasive and less-invasive routes

Invasive operations, such as surgery, are important in healthcare that requires the use of advanced high-end surgical devices [34]. Some procedures, especially more recent ones, may take longer [35]. Most pain is caused by wounds from an incision, which is a vital part of the operation [36]. There is some pain and nausea with laser therapy, radiofrequency therapy, etc. [37]. In addition, certain operations can usually cause some pain in the patient at first, and some side effects can last for a day or two that do not require hospitalization [38]. Therefore, non-invasive surgery is much simpler to heal compared to invasive surgical operations [39].

Patients with non-invasive surgeries need not require any additional assistance at home, because in most situations, regular tasks can be resumed within a few days. There are no scalpels or incisions for non-invasive treatments. This eliminates the need for stitches and, most importantly, eliminates the possibility of scarring. Most invasive operations leave tell-tale marks. When patients are released from the hospital after a surgical operation, they are often administered antibiotics to avoid infection. In the event of complications, they are also sent off with a list of responses to look out for. While both operations have a risk, non-invasive procedures have a relatively low risk of going wrong [40]. Surgeries can necessitate the presence of a team of support personnel, such as an anaesthetists, nurses, and technicians, both during and after the surgery. The treatment is also less difficult since non-invasive treatments are practically painless [41] and there is no risk of an emergency occurring. This usually translates to a cheaper price. This article reviews different approaches of insulin delivery in the non-invasive route, including transdermal, oral, vaginal, nasal, and ocular.

5. Non-invasive routes of insulin delivery

5.1. Oral

Non-invasive insulin delivery by oral route has been recognized as the most preferable by patients since many years ago [42]. This route consists of the lips to the oropharynx (100 cm^2) [43]. The oral mucosa is made of epithelium, connective tissue, lamina purpura, and adipose tissue. Saliva dilutes and the mucin in saliva creates a barrier for insulin permeation [44]. The absorption of insulin occurs by permeability across the mucosa (Fig. 3). Insulin cannot reach the epithelial cells due to the mucin blanket which takes the insulin and further reduces the absorption of the drug significantly [43]. In oral delivery of insulin, the thickness of mucosa plays an important role. With the increase in thickness of mucosa, the permeability of insulin lowers drastically [45]. However, a low total surface area in the range of 100–200 cm^2 is the major limitation of this method for oral drug delivery. On the other hand, insulin is susceptible to hepatic first-pass metabolism and will be metabolized in the gastrointestinal (GI) tract mucosa [43]. There are different types of particles which are applied for oral insulin delivery. The most common carriers are listed as follows.

PEG nanoparticles are synthetic polymers currently popular for drug delivery applications in cancer therapy [46]. PEG is a hydrophilic, nontoxic, nonimmunogenic, highly water-soluble, and protein-resistant polymer. These qualities make it the best polymer for biological incorporation. PEG provides a protective coating of nanocarriers to deliver therapeutic agents under various physiological conditions [28]. The conjugation of PEG with a bioactive substance allows for more modification of its appropriate size, physicochemical properties, and higher retention time of the therapeutic agent in vivo. Various nanoparticles and biomolecules are isolated by antibodies and proteins which accelerate their clearance by mononuclear phagocytosis system [47]. The PEG layer on the nanoparticles creates a rigid barrier around the nanocarriers, preventing the photochemical processes of the nanoparticles and prolonging their retention time in the body. PEG nanoparticles exhibit appropriate physicochemical behaviour, high biocompatibility, and improved serum stability [48].

The efficacy of d-α-tocopherol poly(ethylene glycol) 1000 succinate (TPGS)-emulsified PEG-capped poly(lactic-co-glycolic acid) (PLGA) nanoparticles as potential drug carriers for oral delivery of insulin was studied [49]. Serum glucose was significantly reduced with these nanoparticles, and a 3-fold decrease was observed with insulin-loaded PLGA nanoparticles compared to diabetic rats treated with free insulin. The results showed that oral administration of TPGS-emulsified PEG-capped PLGA nanoparticles is an effective way to lower serum glucose levels within 24 h. Histopathological studies have shown that these nanoparticles can repair streptozotocin-induced damage in the pancreas, kidney, and liver, and exhibit biocompatibility and regenerative effects. It was concluded that PEG could act as a potential drug carrier for oral delivery of insulin.

Liposomes are well-investigated and the most common nanocarriers

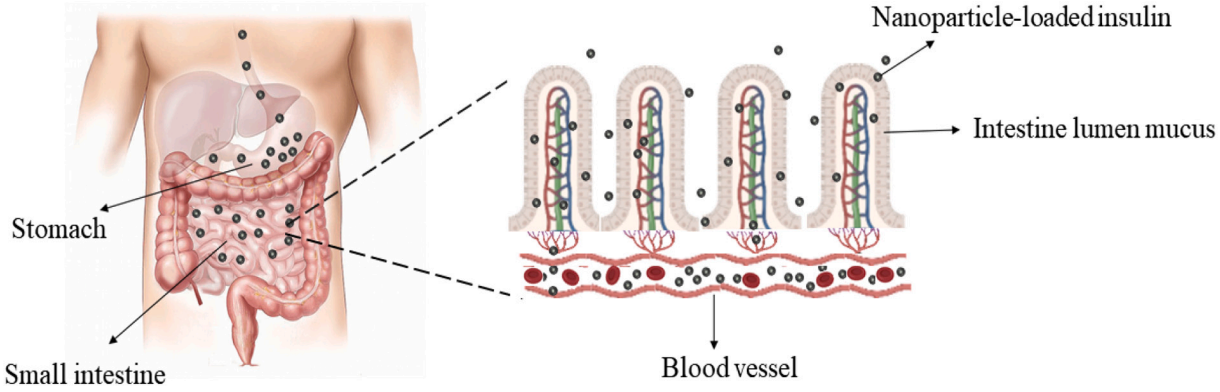

Fig. 3. Oral insulin delivery methods.

for targeted drug delivery [50]. They improved therapeutics for a wide range of biomedical applications by stabilizing therapeutic compounds, overcoming barriers to cellular and tissue absorption, and improving delivery of compounds to target sites in vivo. Liposomes are defined as phospholipid vesicles made up of one or more concentric lipid bilayers containing discrete water spaces [51]. The unique ability of the liposomal system to remove hydrophilic and lipophilic compounds allows a wide variety of drugs to be encapsulated by these vesicles. Hydrophobic molecules are introduced into the bilayer membrane, and hydrophilic molecules can be trapped in the aqueous centre. As a drug delivery system, liposomes offer several advantages, including biocompatibility, self-assembly, ability to transport large volumes of drug, and a wide range of physico-chemical and biophysical properties that can be modified to control their biological properties [52]. Encapsulation in liposomes protects compounds from inactivation, degradation, and dilution in the circulation. Liposomes are generally considered to be pharmacologically inactive with minimal toxicity, as they tend to consist of naturally occurring phospholipids [50].

A liposomal carrier was created in a study using phosphatidylethanol formed by phospholipase D catalyzed by the transphosphatidylation of phosphatidylcholine for oral delivery of insulin [53]. The obtained liposome was orally administered to rats having a blood glucose concentration of 270 mg/100 ml at a dose of 12 IU/kg body weight. Oral administration of all types of liposomes resulted in hyperinsulinemia. Hyperinsulinemia due to liposomes containing dipalmitoyl phosphatidyl ethanol was accompanied by a decrease in blood glucose concentration.

Alginate is a biomaterial that has found many applications in biomedical science and engineering due to its favorable properties, including ease of gelation and biocompatibility [54]. Alginate hydrogels have been of particular interest in wound healing, drug delivery, and tissue engineering applications, as these gels retain structural similarity to the extracellular matrix in tissues and can be manipulated to perform many essential roles. Alginate hydrogels can be prepared by a variety of crosslinking methods, and their structural similarity to the extracellular matrix of living tissue allows for a wide range of applications in wound healing, providing biologically active agents such as small chemical drugs and proteins, and cell transplantation [55]. Alginate wound dressings maintain a physiological micro-humidity environment, minimizing bacterial infection in the wound, and facilitating healing. Drug molecules, from small chemical drugs to macromolecular proteins, can be released from alginate gels in a controlled manner, depending on the type of crosslinking agent and the crosslinking method. In addition, alginate gels can be administrated orally or injected into the body in a minimally invasive manner, allowing for wide applications in the pharmaceutical field [56]. Traditional wound dressings (e.g., gauze) primarily provide a barrier function – keeping the wound dry by allowing secretions to evaporate while preventing the entry of pathogens into the wound. In contrast, modern dressings (e.g., alginate dressings) create a moist environment for the wound and facilitate wound healing [57]. Alginate dressings are typically manufactured by ionic crosslinking of alginate solutions with calcium ions to form a gel, which is then processed to form lyophilized porous sheets (i.e., foam), and fibrous non-woven dressings. Alginate dressings in dry form absorb wound fluid to coagulate, and the gel can then supply water to dry wounds, maintain physiological micro-humidity environment, and minimize wound bacterial infection. These functions can also promote granulation tissue formation, rapid epithelialization, and wound healing [54].

Alginate is a natural polymer, extracted from algae, that has the ability to form a gel when dissolved in water and exposed to certain salts [58]. Gelation can be performed to produce wet or dry spherical beads for visual effects, encapsulation of other materials or agglomeration of powders. A typical experimental procedure involves adding an alginate solution to a drug suspension [59]. Furthermore, the mixture is added dropwise to the calcium chloride solution. As a result, an alginate hydrogel is formed by encapsulating the drug in suspension by interaction with the calcium chloride solution. This approach has been used to improve the delivery of orally encapsulated Nystatin [60]. Excellent biodegradability and biocompatibility are observed with alginate beads, microcapsules, and pellets, making them very useful in medicine and as a drug delivery system. Alginate beads are one of the most used carriers for cell immobilization. They offer several advantages as a carrier, such as good biocompatibility, low cost, ease of availability, and ease of preparation [61]. However, there are some limitations associated with their use, such as gel degradation, severe mass transfer limitations, large pore size and low mechanical strength (causing release of cells from the carrier) [58].

A pH-responsive composite hydrogel bead composed of κ-carrageenan and alginate was formed and tested as a carrier for oral delivery of insulin [20]. The hydrogel beads assembled at pH 1.2 successfully retained insulin through electrostatic interaction between the negatively charged sulfate group of the κ-carrageenan and the positively charged insulin. At pH 7.4, insulin was released gradually, and as the concentration of κ-carrageenan used for hydrogel bead formation increased, the release profile approached zero-order kinetics. The results indicate that alginate/κ-carrageenan composite hydrogel beads are a promising oral insulin delivery system. Insulin was encapsulated in calcium alginate beads coated with chitosan [62]. Its release from alginate-chitosan-glutaraldehyde and alginate-chitosan beads was studied in artificial gastric (pH 7.5) and intestinal (pH 1.2) fluids. By comparing the release amounts, the ionic interaction between medium pH with the alginate-chitosan matrix, the intestinal fluid was found to be better. The degradation of the released insulin was also investigated. The granules remained stable even after 6 h of incubation and undigested insulin was sufficient for physiological conditions. Therefore, this system can be proposed for oral delivery of insulin.

Salecan is made from polysaccharide and is a non-ionic polysaccharide. This polysaccharide has important physicochemical

properties [63]. For example, salecan has superior rheological properties and the ability to form high viscosity solutions at low shear forces and concentrations, high viscosity yield values as well as high pseudoplasticity. Salecan also exhibits attractive biological characteristics such as biocompatibility and biodegradability [64]. These characteristics make salecan the material of choice for many applications including tissue engineering, drug delivery, biosensors, and water purification [65]. In addition, due to the presence of different derivable groups (e.g., hydroxyl group) on the backbone of salecan, it can be easily tuned chemically and biochemically, providing greater flexibility and convenience for making certain materials with a targeted function. All these advantages make salecan polysaccharides very attractive for the design of biomaterials. The main limitation of salecan-based hydrogels as a drug delivery platform is the difficulty in controlling their degradation [63].

A salecan-based hydrogel was performed for oral delivery of insulin. The in vitro insulin release profile showed that the release of entrapped insulin was inhibited under acidic conditions but significantly increased at neutral pH. Oral administration of insulin-loaded salecan hydrogel to diabetic rats resulted in a sustained decrease in fasting blood glucose levels over 6 h of administration. The results simulate further development of salecan-based hydrogels as carriers for controlled delivery of insulin after oral administration [66].

PAA is considered a primary mucosal adhesion polymer and the protonated form at acidic pH is responsible for mucosal adhesion [67]. PAA forms hydrogen bonds between the –COOH groups and the sialic –COOH groups of the mucin glycoprotein. This bond formation leads to increase in the viscosity. Therefore, these acrylic compounds can also be used as hydrogels to treat ocular irritations. The high-water solubility of PAA may cause it to dissolve before the desired time for the drug to penetrate membrane [68]. These polymers have been shown to partially inhibit the bioactivity of enzymes in the GI tract by binding to Ca^{2+}, which is involved in the activity of several proteolytic enzymes [69]. In addition, hydrogels based on these polymers have shown pH-responsive swelling-deswelling transitions due to ionization-deionization of the carboxylic acid groups. As a result, the drug loaded in the gel can be protected in the acidic environment of the stomach but is rapidly released in the neutral conditions of the small intestine. These materials may be ideal candidates for an oral delivery system, as pH changes in the GI tract may be responsible for stimulating controlled release [69].

An oral insulin delivery system was developed using thiol-functionalized hydrogel microparticles based on polymethacrylic acid/PEG/chitosan [70]. Thiol modification was achieved by grafting cysteine to the activated surface carboxyl groups of the hydrogel. In this study, microparticle-assisted hydrogel thiolation was shown as a promising oral delivery mode of peptides/proteins.

Oral insulin release can be improved using biotinylated liposomes. Liposomes have shown their ability in oral insulin delivery due to ease of absorption and protection of the payload from the harsh GI environment. Biotin (vitamin B7) cannot be produced by the human body itself. Biotin receptors are non-specific and can be found throughout the small intestine, allowing the absorption of biotin via the GI tract through Na^{+}-dependent and carrier-mediated endocytosis. Integrating biotin-conjugated phospholipids into the membranes of the liposome produces biotinylated liposomes [71]. Liposomes have shown their high ability in oral insulin delivery because of their capability to facilitate absorption process and to defend the burden from the unpleasant GI surroundings. Commonly, cholesterol liposomes or phospholipids are easily damaged to demolition by GI enzymes or gastric acid, causing decreased oral bioavailability [72]. The liposome membranes are biotinylated by incorporating biotin-conjugated 1,2-distearoyl-sn-glycero-3-phosphatidyl ethanolamine into them [73]. Liposome biotinylation can improve cellular absorption of encapsulated molecules.

pH-responsive systems have attracted significant interest among all types of smart hydrogels due to their potential application in pharmaceutical sectors [74]. The pH-sensitive systems have shown good potential for delivery of bioactive proteins or peptides of insulin via oral systems [75]. In this method, carboxylic acid groups with Ca^{2+} binding obstruct the bioactivity of enzymes in the GI pathway [76]. By organization of polypeptide molecular weights, some additional accurate systematic configurations are found. Poly(L-glutamic acid) (PGA) are important pH-responsive polypeptides due to their biodegradability and biocompatibility nature. These hydrogels do not have enough hydrophobic ability to protect the biodegradation of PGA chains at acidic pH conditions, which may affect early insulin release and demolition of proteins in the GI tract. Thus, hydrogels composed of higher hydrophobicity components such as PGA [77] have been developed in the recent past to overcome this drawback [78]. In addition to pH-sensitivity, the insulin release profiles from the hydrogels can be regulated by varying the swelling ratio in the stomach and intestine. In artificial gastric fluid with pepsin (pH 1.2), the rate of biodegradation and insulin release is much slower [79]. However, in artificial intestinal fluid with pancreatin (pH 6.8), these functions are greatly improved. A continuous hypoglycemic effect was observed after oral administration of insulin-loaded hydrogel particles to streptozotocin-induced diabetic rats.

Insulin-loaded microparticles were prepared using alginate and whey protein by following cold gelation method [80]. These microparticles and liposomes were developed to increase the oral bioavailability of insulin and to continue insulin action [81]. Whey proteins, chitosan, and alginate were acknowledged for demonstration of mucoadhesive to the mucosal tissue that enhance the interaction time of insulin with mucosa [82]. Insulin encapsulation with whey protein and alginate hydrogel microparticles directed to a substantial rise of the oral bioavailability [82]. In this situation, insulin oral bioavailability appeared to be connected to both the mucoadhesive characteristics of the polymers and their enzymatic inhibition abilities [83]. Whey proteins, both as microparticles and formulations, were developed to increase the insulin penetration into transepithelial electrical resistance [84]. This polymer combination could be administered in an enteric coating capsule and considered a promising technique for improving in vivo insulin delivery efficacy [80].

In stimuli-sensitive drug delivery systems, insulin is trapped in a network of glucose-responsive elements including enzymes (glucose oxidase/catalase and glucose binding proteins) [85]. The matrix often responds to structural changes that are followed by the change in glucose concentration, resulting in glucose-stimulated insulin release [64]. Most current synthetic closed-loop structures have reduced flexibility due to their low biocompatibility and administration process. In contrast to chemically synthesized macromolecular products, peptides as the molecular building blocks for self-assembly allow easy incorporation of bifunctionality into materials, biocompatibility, biodegradability, ligand identification, and injectables [86]. Due to enzymatic degradation in the GI tract and low absorption through the intestinal membrane, large molecular weight peptides and proteins have poor oral bioavailability. Insulin is rapidly digested by enzymes which further leads to the decrease in active insulin concentration in the stomach. The development of a stimuli-responsive drug delivery mechanism for controlled release is encouraging [87]. Various drug carriers can be used to protect insulin in low pH conditions or enzymatic digestion in the stomach. Therefore, they can release and absorb insulin through the small intestine into the bloodstream [88].

Stimulus-responsive polymeric hydrogels are exciting and appealing delivery carriers for protein/peptide products as they allow for dosage and spatiotemporal control of protein/peptide delivery. A series of new salecan-based pH-sensitive hydrogels for controlled insulin delivery were formed using the graft copolymerization reaction between salecan and 2-acrylamido-2-met. Salecan produced by *Agrobacterium* sp. is a polysaccharide composed of β-1-3-linked glucopyranosyl and α-1-3-linked units. Salecan showed notable nontoxicity and antioxidant properties [89]. Poly(2-acrylamido-2-methyl-1-propane sulfonic acid) (PAMPS) can donate or accept protons upon the environmental

transform in pH [90]. Furthermore, the hydrophilic sulfonate groups of PAMPS can pair with other bioactive moieties including carboxylate and amino functional groups, acting as an ion exchange site [91]. These characteristics make PAMPS a valuable candidate for site-specific insulin delivery and feedback regulation [92]. The glucose-sensitive insulin delivery system is made up of a pH-sensitive peptide hydrogel, encapsulated insulin, and enzymes that can transform glucose to gluconic acid and then change the pH of media [93]. Electrostatic repulsion occurs as the pH drops below the pKa of lysine/ornithine side chains, causing individual hairpins to unravel. In vivo tests have shown that the hydrogel is biocompatible, injectable, and effective at regulating blood glucose levels over time [64].

Polymeric hydrogels have shown their ability for insulin transportation in a regulated manner [94]. Chitosan is a naturally occurring linear binary cationic polysaccharide resulting from the alkaline hydrolysis of chitin. It is made up of D-glucosamine and *N*-acetyl D-glucosamine repeating units bound by a β-(1 → 4)-glycosidic linkage. The pH-sensitive beads are prepared by interpenetrating polymer networks of carboxymethyl chitosan and alginate [94]. Since oral insulin delivery necessitates a more efficient and pH-sensitive polymeric method, alginate is used as a biopolymer to improve oral delivery success. Alginate, a water-soluble linear polysaccharide, is derived from brown seaweed that contains varying concentrations of 1,4-linked b-D-mannuronic acid and a-L-guluronic acid residues. These interpenetrating polymer network beads were utilized to encapsulate insulin. Immunogenicity with no toxic effect on animals, biodegradability, and biocompatibility are some of the major characteristics of this polymer [94]. To attain the desired functions, the bioavailability of insulin after oral administration should be maintained. These beads had an effective protector to insulin during the cross over the inferior pH environment of the inside GI tract [95]. At gastric pH, the prepared beads successfully protected insulin, while at pH 6.8 (duodenal pH) and pH 7.4 (intestinal pH), a large amount of insulin is released. The released insulin was stable and biologically active after encapsulation. These polymeric formulations created in an aqueous medium are a crucial fact for this complex [94].

Table 1 summarizes oral insulin delivery methods in various studies. Oral insulin delivery was effective at concentrations of minimum 5 and maximum 47 IU/kg. The required time was in the range of 1–25 h with 96% maximum insulin release for the thiolated chitosan nanoparticles.

5.2. Transdermal

Transdermal delivery is proved as one of the most favorable methods for novel drug delivery systems [104]. As the insulin dispensed by the transdermal delivery system avoids the GI tract which inhibits transformation by the liver, there are less chances of liver dysfunction and GI tract irritation as side effects [105]. Insulin delivery through the skin (Fig. 4) has some benefits such as keeping an effective rate of insulin in a period, circulating a steady rate, exploiting the passive delivery system, and diffusion [106]. Injection aids are presently in practice to diminish the incidence of needle obsession and multiple injections to a diabetes patient [107]. The chemical agents have been applied over the skin for the purposes such as cosmetics, healing, and protective aims for many years [108]. In this method, insulin invasion is driven by Fickian diffusion into the skin layers of the stratum corneum, epidermis, and dermis. The stratum corneum is the outermost thickness of the skin, about 10–15 mm of tissue, and is recognized as the primary barrier to insulin infusion. To overcome this obstacle, microneedles with tiny and short needle arrays are created to straight penetrate the stratum corneum of the skin [109]. Once the microneedle is applied to the skin, it punctures the epidermis and reaches to the dermis. This technique can increase patient compliance and tolerate painless delivery due to the depths of needle insertion within the non-innervated layer of the skin [110]. There are different types of carriers which are applied for transdermal insulin delivery. The most common carriers are listed as follows.

Pectin, an edible plant polysaccharide, has been shown to be useful in building drug delivery systems for the delivery of specific drugs [111]. It is non-toxic and stable throughout the GI tract, where degradation can only be initiated and continued only by the colonic microflora [112]. These advantages of pectin have led to development of pectin-containing drug carriers for safe transdermal drug delivery. However, once it reaches the colon, it changes its consistency and is destroyed by bacteria in the colon [113].

Microneedles are microscopic structures designed to puncture the

Table 1
Summary of oral insulin delivery methods in various studies.

Insulin carrier	Insulin concentration (IU/kg)	Insulin release (%)	Duration of release (h)	Remarks	Ref.
Thiolated *N*-dimethyl ethyl chitosan	5	84	8		[96]
Choline and geranate ionic liquid	10	20	5	An ionic liquid-based oral insulin formulation that greatly improved oral insulin absorption by effectively circumventing gastrointestinal barriers.	[97]
Crystalline mesoporous metal–organic framework	37	10	1	Insulin maintains most of its activity. It can withstand extreme environments when producing insulin in a stomach-like condition.	[98]
Chitosan/alginate nanoparticle system by forming cationic β-cyclodextrin polymers	45	40	2	Total insulin release was much greater than in the absence of cationic β-cyclodextrin polymers. The structure of insulin was well preserved during the release process and nanoparticle preparation.	[99]
Microemulsion + albumin and piperine	25	78	25	The stability of gastrointestinal improved enzyme protection. Storage resistance.	[100]
Chitosan-phytic acid microspheres crosslinked with phytic acid	14	87.2	8	Entrapment efficiency. In the gastric fluid, there was no insulin blast release. Intestinal medium: long-term release. Steady hypoglycaemic effect in diabetic rats.	[101]
Carboxymethyl β-cyclodextrin grafted carboxymethyl chitosan hydrogels	47	70	7	Hydrogels targeting insulin released from them are non-cytotoxic and have exceptional stability. The insulin-containing hydrogel microparticles had a strong hypoglycaemic effect and maintained a higher level for a long time.	[102]
Thiolated chitosan nanoparticles	20	96 92	12 24	The decreased and increased levels of insulin and glucose, respectively in streptozotocin-induced were better than any other therapies in the rats.	[103]

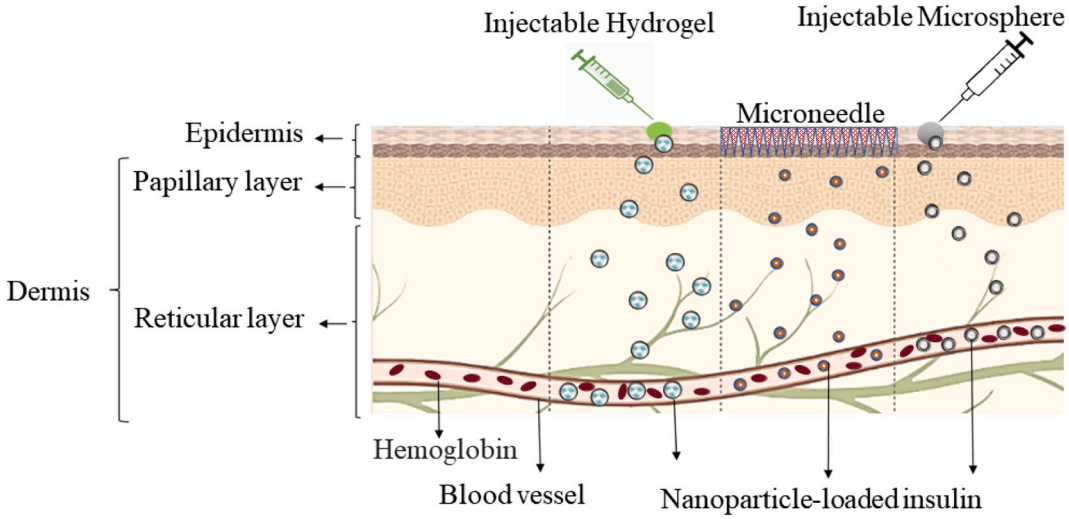

Fig. 4. Transdermal insulin delivery methods.

stratum corneum and allow drug delivery into the epidermis or dermis [114]. The insertion of microneedle tip into the skin forms temporary microparticles, facilitating drug delivery that cannot passively diffuse across the stratum corneum [115]. First-generation microneedles, made from silicon, metal or organic polymers, are designed to create the pores in the skin for the drug or vaccine to diffuse in. Dissolved microneedles are typically created by moulding processes using a limited number of processes. The complete filling of micromolds with formulations is limited by the surface tension between the solution and the high micrometer-scale mold. Inadequate filling leads to improper microneedle formation, the appearance of air bubbles or failure to remove the dissolved microneedle from the mold [116]. A major barrier to the successful translation of biodegradable microneedles is the ability to manufacture these drug delivery systems on a large scale. However, the most used production methods are batch methods, which can pose barriers to scaling for efficient and high-throughput continuous production processes [117].

Injectable hydrogels have been extensively studied for use as scaffolds or as carriers of therapeutic agents such as drugs, proteins, cells, and bioactive molecules in the treatment of diseases and cancer as well as in repair and tissue regeneration [118]. The amorphous hydrogel is applied liberally onto or within the wound and covered with a secondary dressing such as foam or film. The hydrogel can remain in situ for up to 3 days. Hydrogel is indicated in dry, porous wounds with light exudate and partial thickness wounds [119]. Injectable hydrogels have certain advantages, such as being able to reach very deep tissue defects, have excellent adaptability to defect margins, are minimally invasive, and complete the filling of defects leading to neovascularization of healthy tissues [120].

Microgels are colloidal gel particles made up of chemically crosslinked three-dimensional polymer networks. They can swell or shrink in response to a variety of external stimuli such as ionic strength, temperature, pH, enzymatic activities, and electric field [121]. Hydrogel microparticles (microgels) are currently the subject of extensive research for drug delivery and controlled release of bioactive molecules [122]. Biopolymer-derived microgels are hydrophilic crosslinked polymer networks. Their structure is very similar to solid particles, once their surface is well established. These gels have high water capacity, large surface area, and internal network useful for drug delivery system [122].

Injectable microspheres are prepared using a very small, hollow, round bead made of glass, ceramic, plastic, or other materials [123]. The microspheres are free-flowing particles ranging in size from 1 to 1000 μm [124]. Microspheres have wide applications in drug delivery systems. They are mainly used for targeted drug delivery of anti-cancer agents and ophthalmic drugs and can be used for diagnostic purposes. Microspheres used to manufacture and test medical devices are generally solid particles made from strong and durable raw materials such as polymers, glass, and in some cases ceramics [125]. The spheres can be produced from pre-existing linear polymer chains or can be formed during polymerization from monomer solution [126]. Microspheres can encapsulate many drugs including small molecules, proteins, and nucleic acids and are easily administered with a needle. In general, they are biocompatible, can provide high bioavailability, and are capable of sustained release over long periods of time [126].

Stimuli-responsive hydrogels formed by various natural and synthetic polymers can show changes in their properties to external stimuli such as light, temperature, pH, ionic change, and redox potential [127]. Glucose-responsive hydrogels have been investigated for self-regulating insulin release for the treatment of diabetes [128]. These glucose-responsive hydrogels are biologically sensitive to glucose and ambient pH and deliver the appropriate amount of insulin in response. The structure and specificity of glucose-responsive hydrogels have been shown to mimic the functional basis of insulin release from the pancreas [129].

The supramolecular hydrogels formed by assembling molecular building blocks known as hydrogelators also exhibit stimuli-responsive properties [130]. Although supramolecular hydrogels show many of the same functions as conventional polymeric hydrogels, the lattice formation in supramolecular hydrogels is different from that of conventional polymeric hydrogels [74]. In the first case, the network formation is purely through non-covalent interactions while polymeric hydrogels are usually formed by chemical crosslinking. In the case of supramolecular hydrogels, low-molecular-weight hydrogels assemble through non-covalent interactions (hydrogen bonding, electrostatic interactions, hydrophobic interactions, van der Waals interactions, and π–π interactions) in structures such as nanofibers and the helices, leading to entangled networks immersed in water [131]. Supramolecular hydrogels, which perfectly combine the advantages of synthetic hydrogels with those of supramolecular polymers, are a new type of non-covalent crosslinked polymeric materials. Supramolecular crosslinking by various non-covalent interactions such as hydrogen bonding, metal–ligand coordination, host–identification, and electrostatic interactions greatly reduces the structural flexibility and macroscopic performance, leading to the formation of 3D crosslinked networks. In contrast, these noncovalent hydrogels not only show moderate mechanical properties obtained from the polymeric building blocks, but also exhibit reversible sol-gel transition behaviour for the reaction with a wide range of biological stimuli (e.g., pH, redox agents, enzymes, molecular bioactivity).

Processing capabilities inherent in supramolecular crosslinking units may play a role as intelligent carriers to deliver versatile therapeutic agents (e.g., drugs, genes, proteins) or promising substrates for repair and regeneration of human tissues and organs [130].

Injectable in situ gel-forming systems have become a common alternative delivery method for peptides and proteins because of their ease of manufacture, lack of organic solvents, ease of sterilization by filtration, and medical applications [132]. At low temperature, polymer system appears as a liquid, while with rise in temperature it turns into a gel. It can be quickly entrapped into thermo gels without any loss of insulin simply by combining insulin with the polymeric sol at a low temperature. Subsequent injection of insulin-containing sol, a physical hydrogel is formed in situ at body temperature. PLGA-PEG-PLGA triblock copolymers are the most common biodegradable thermogel due to their tunable biodegradability and good safety profile [133]. The hydrogel matrix greatly improved the stability of insulin [133]. As a result, the injectable, biodegradable, and thermosensitive hydrogel has a lot of potential as a delivery mechanism for better patient compliance [134].

Dissolving or biodegradable microneedles have a lot of coverage as they can penetrate the stratum corneum and enter to the epidermis and dermis after insertion into the skin. Besides, they can completely dissolve or eventually degrade to release the narcotics, without any waste in the skin. Drugs such as insulin can be delivered using dissolving microneedles as a secure and convenient transdermal method [135]. A multi-layered pyramidal dissolving microneedle patch consisted of silk fibroin tips with high mechanical strength. Gradual dissolution and insulin release supported by a flexible polyvinyl alcohol (PVA) can improve insulin delivery [136]. The gelatin microneedle patch can promptly be soluble in the skin interstitial fluid. Insulin is released from these encapsulated microneedles by dissolving after insertion into the skin [137]. The results suggested that the novel microneedles can be a very effective substitute for transmitting insulin from the skin to the systemic circulation without causing any injury to skin [138].

It should be noted that the pure gelatin hydrogels have poor mechanical strength and shape consistency. Physical gelatin and starch mixing is a simple and inexpensive way to increase the consistency and mechanical power of gelatin [135]. The gold nanomaterials as additives improved the mechanical strength of the microneedles, allowing them to efficiently penetrate the skin. Further, gold nanocarrier drugs in the microneedles allowed glucose-responsive insulin release activity without apparent toxicity in vivo [139].

Microgels are solvent-swollen networks and known to be a promising material for insulin delivery that can discrete particles in the range of 20–50 mm [140]. The advantages of insulin delivery using microgels are bioaccumulation and degradation, ease of synthesis, biocompatibility, reliably regulating insulin binding and release kinetics, long-term longevity, shelf-life, and control over basic characteristics such as size and functionality [141]. In addition, their water-swollen networks present low interfacial energy, which shows higher hydrophilicity in biological media. It cause increasing bioavailability, biocompatibility, and reduced nonspecific interactions with proteins [142]. The microgels can deliver the low-molecular-weight medications such as dexamethasone and bupivacaine [143], and biomacromolecules such as fluorescein-labelled dextran, bovine serum albumin (BSA), and insulin [121].

Temperature sensitive biodegradable block copolymer–based hydrogels are a common choice among physically crosslinked injectable systems. Bulk copolymerization of ring-opening formed a triblock copolymer of PEG-PCL-PEG (PECE). They were converted into hydrogel because of the associated micelle development and formation of hydrophobic interaction [144]. The lack of covalent crosslinking and biodegradability of the polymer allows for easy removal from in vivo systems [61,96]. In comparison to glycolide and lactide block copolymer hydrogels, PECE powder presents brittle properties and is therefore easily weighed [28]. PECE forms a solid hydrogel-like structure than Pluronic due to its crystalline structure [141]. Insulin retains its secondary structure after controlled release. The polymer concentration and the initial insulin loading concentration can also be changed to control the insulin release [145]. For diabetic recovery, PECE hydrogel based temperature-responsive pulsatile insulin release has shown promising results [146].

Genipin, an aglucone of geniposide, is a component of Chinese medicine [147]. Genipin can react spontaneously with primary amine and has 5000–10,000 times lower cytotoxicity compared to glutaraldehyde [148]. As a result, intermolecular crosslinks are formed using genipin between classes of primary amines in a variety of compounds [149]. Hence, genipin is used to shape the intermolecular crosslinks between primary amine groups of polymer ligand and Concanavalin A (Con A). It is also effective in immobilizing Con A to the microgel systems and preventing the leakage of lectin [150]. Con A, glucose oxidase, and phenylboronic acid-based glucose-responsive carriers increased swelling ratio in response to variation of glucose concentrations which further leads to self-regulating insulin delivery systems. Self-regulated insulin delivery systems are appropriate for insulin-dependent diabetes patients to maintain a normal blood glucose level, whereas traditional dermal insulin injections typically result in insufficient glycemic control and patient defiance [151]. These glucose-responsive delivery systems are based on glucose oxidase, phenylboronic acid, and Con A [152]. The glucose-responsive system dependent on Con A is the most specific system to glucose. Con A has a higher reactivity with non-reducing α-D-glucose and α-D-mannose than with other forms of the ring [150], that enables it to allow glucose or polysaccharide moieties containing polymer to gel with high affinity [150]. Insulin release is reversible in response to differing glucose concentrations and could be repeated. The released insulin was found to be active without disrupting the tertiary structure [153]. These microgels hold outstanding in vitro biocompatibility and are non-cytotoxic [150]. This microgel may be useful for self-regulating insulin delivery as well as other applications including actuators and glucose-sensitive separation systems [154].

Glucose-responsive hydrogels are very appealing for designing closed-loop structures due to their higher sensitivity to glucose concentration [155]. Phenylboronic acid (PBA) can form a dynamic complex with polyol, such as PVA. In the presence of another opposing polyol, such as glucose, the complex can be dissociated [129]. Because of their capacity to sense environmental changes such as pH, temperature, light, and biomolecules, stimuli-responsive hydrogels are also called as intelligent materials [156]. Hydrogels are generated using this process exclusively by combining β-cyclodextrin, as well as diblock polymer of poly(ethylene oxide)-*b*-polyvinyl alcohol (PEO-*b*-PVA) and PBA with PEO crosslinker [155]. Active covalent bonds between PBA and PVA offer sugar responsive crosslinking, and the inclusion complexation between β-cyclodextrin and PEO can accelerate the development of hydrogel and expand its stability. These glucose-responsive hydrogels are desirable products for improving closed-loop systems [157]. The complex can be separated in the existence of glucose as a competing polyol. The hydrogel device could be used as a glucose-responsive material for insulin delivery. The two effective methods for optimizing the glucose-responsive properties are increasing the proportion of PBA and PVA in the hydrogel system, and expanding hydrogel system to microgel system by miniaturizing their volume [158].

The biocompatible and biodegradable scaffold of chitosan-beta glycerophosphate-hydroxyethyl cellulose (CH-GP-HEC) presents a sol–gel transition at 37 °C [159]. Chondrogenic and mesenchymal stem cells can be inserted into the CH-GP-HEC and implanted into the site to fill cartilage tissue deficiencies with reduced discomfort and invasion. Chitosan-based hydrogels are mostly applied for tissue engineering due to their distinct properties such as no debris or non-toxic by-products formation, high water solubility, biodegradability, and biocompatibility [120]. The cationic nature of chitosan can entrap anionic glycosaminoglycans by electrostatic interactions. Chitosan can be applied to form

an injectable hydrogel either by covalent crosslinking method or physical endothermal process. In combination with a crosslinking agent such as hydroxyethyl cellulose and glycerol phosphate, it can form sol-gel at body temperature [160]. Injectable hydrogels can be introduced to the body with minimal invasiveness using percutaneous or endoscopic techniques [161]. The structure of insulin is the same as insulin-like growth factor 1. In this method, the insulin binds with its receptor and therefore provokes the same impact on cartilage [162]. Insulin is also able to promote the accumulation of matrix, avoid central necrosis, and induce redifferentiation of dedifferentiated chondrocytes [120]. As a result, this kind of hydrogel can be used to fill cartilage defects with encapsulated mesenchymal stem cells during arthroscopic procedures. This ability is vital for optimizing mesenchymal stem cells as a feasible cartilage engineering alternative to chondrocytes [163].

Amidated pectins are low methoxyl pectins with amidated carboxylic acid groups. They are more resistant to pH changes and calcium levels than traditional pectins [164]. According to earlier studies, pectin (polygalacturonic acid) not only transports insulin to the colonic part of the GI tract, but also maintains insulin release in vitro. [164]. Preparation of an insulin-containing pectin dermal patch is capable of transporting insulin through the skin and withstanding regulated release into the bloodstream of diabetic rats caused by streptozotocin. Insulin passage through this route is active due to its ability to lower blood glucose concentrations [113]. Additionally, the reduced insulin responsiveness in muscle during diabetes has highlighted the key role of insulin in hepatic glucose homeostasis [164]. The cellular and biochemical effects of insulin are facilitated by the insulin receptor, and are available in nearly all vertebrate tissues including skin [113]. This method indicated that an insulin-containing dermal patch formulation could provide gradual regulated release of insulin and a great relieve to a variety of diabetic symptoms [112].

Supramolecular hydrogels are a type of physical hydrogels in which the network development is based on the noncovalent interactions of polymer fragments such as hydrophobic interactions, π–π interactions, hydrogen bond, and cation–π [119]. Direct encapsulation of growth factors or cells inside supramolecular hydrogels is one strategy for therapeutic delivery from supramolecular hydrogels which include enzymatically or hydrolytically degradable crosslinks to regulate the release [165]. The formed supramolecular hydrogels by polymers and cyclodextrins have been used as manageable insulin delivery systems [166]. In this type of hydrogels, chemical crosslinkers help in maintaining the chemical gel morphology among hydrophilic molecules [167]. Cyclodextrin is a sequence of cyclic oligosaccharides consisting of a macrocyclic ring of glucose subunits correlated by α-1,4-linkage [168], which is subsequently supramolecular. Molecular complexes tend to aggregate to form hydrogels [127,128]. Supramolecular hydrogels have been assessed as proficient insulin carriers, because of their consistency, biocompatibility, and high-water content [167]. The developed composite is injectable, shear-thinning, self-healing, and appropriate for insulin delivery [170].

Transplantation of insulin producing cells have been explored for the treatment of type-1 diabetes [171]. Direct cell implantation has a limited role in diabetes care due to the need for host perception of transplanted cells, intensive immunosuppressive therapy, and reliance on donor cells [172]. As a result, another approach encapsulates pancreatic β-cells in semi-permeable biomaterials, which separate and hold them from the immune system. At the same time, it allows the distribution and transfer of oxygen and nutrients to the encapsulated cells [173]. Withdrawal of cell-capsule implantation usually necessitates a surgical procedure. More fundamentally, exposure to the outer tissues, the proliferation of alien body giant cells, chronic inflammation, inability of the implant to regulate glucose, and fibrosis reduce the biocompatibility of the cell capsules [174]. This approach incorporates both synthetic glucose-responsive systems and live (cell-based) techniques to secrete insulin through the microneedle. This also enables β-cell capsules that are placed on the outside of the body to detect glucose signals in a minimally invasive manner. To well activate the cellular response, the microneedle composite exclusively comprises synthetic "glucose-signal amplifiers". Self-assembled polymeric nanosized vesicles containing three enzymes, glucoamylase, α-amylase, and glucose oxidase, were used to create glucose signal amplification. The enzyme glucose oxidase converted glucose to gluconic acid in the presence of oxygen [134,135].

These types of polymeric vesicles are self-controlled by a block copolymer integrated with phenylboronic ester (PBE) and PEG conjugate polyserine (mPEG-*b*-P(Ser-PBE)) and were filled with insulin and glucose oxidase. Polymeric vesicles served as the insulin release actuator and the glucose sensing ingredient providing both basal insulin release and inducing insulin release in response to hyperglycemia [175]. Glucose-responsive moieties such as glucose binding proteins, glucose oxidase, or phenylboronic acid were usually consumed by the matrix PBA [137–139] to influence the amount of release of preloaded insulin through glucose binding resistance, polymer degradation, or structure transfer. Due to the fast switching of physiological pH in vivo, such systems were not perfect [176]. However, the presence of hydrogen peroxide (H_2O_2) in this device raised concerns about long-term biocompatibility.

Table 2 presents a summary of data about transdermal insulin delivery methods. Transdermal insulin delivery was effective in concentration range of 5–20 IU/kg. In addition, the required time was in the range of 8–24 h with the highest release of insulin by 100%.

5.3. Nasal

Nasal delivery is a convenient and non-invasive method to bypass the blood-brain barrier and to provide a sufficient systemic drug delivery process [183]. Since blood is pumped straight from the nose into the systemic bloodstream, insulin distribution by the transnasal route has the benefit of bypassing first pass metabolism by the liver (Fig. 5). The nasal cavity has a pH 5.5 [184] and temperature 33–35 °C in humans. The nasal drug delivery system adopts distribution of numerous protein and peptide compounds including insulin for systemic medication. The need for high water solubility and short retention time has been known as the major limitations in nasal drug delivery [185]. In general, persistence of insulin in nasal mucosa is around 15–30 min. Numerous approaches such as microspheres, nanoparticles, bio-adhesives, and co-transporter of permeation promoter with enzyme inhibitors have been suggested to increase the bioavailability of nasal protein drug delivery [186]. There are different types of carriers which are applied for nasal insulin delivery. The most common carriers are listed as follows.

Starch nanoparticles are defined as particles with at least one dimension less than 1000 nm but larger than a single molecule [187]. In addition, dimensional requirements are often more stringent, requiring at least one dimension not to exceed 300 nm. It has many advantages such as high performance and scalability, reproducibility, and encapsulation efficiency [188]. The nature of starch makes it a non-toxic, highly biocompatibility material and poses no danger to human health. Starch is biodegradable, abundant, and renewable in nature. It can be easily modified due to the presence of multiple hydroxyl groups on its main components (amylose and amylopectin) [187] and have a large surface area per volume. These nanoparticles yield of varying crystallinity and size [188]. On the other hand, there are certain limitations to starch nanoparticles as natural starch has low tolerance to many processing conditions (temperature, pH, pressure). Natural starches exhibit low solubility and retrogradation limiting their functional properties. Modification of starch often requires the use of solvents that can produce end products under undesirable conditions [188].

Chitosan is a natural cationic copolymer of great interests for hydrogel structures [58,188]. This polymer is hydrophilic in nature with the ability to degrade through human enzymes, resulting in biocompatibility and biodegradability, two biological properties commonly

Table 2
Summary of transdermal insulin delivery methods in various studies.

Insulin carrier	Insulin concentration (IU/kg)	Insulin release (%)	Duration of release (h)	Remarks	Ref
Microwave treatment	12	49.33	15	Microwave alone promotes skin insulin transfer with no accumulation of barrier residues.	[177]
Chitosan-covered mesoporous silica-coated alumina-based microneedle	20	20	8	Extended glucose control. Regular adjustment of glucose tolerance with no risk of hypoglycemia at the typical condition.	[139]
Self-administrative powder-carrying microneedles	20	100	24	A longer insulin release profile that could be used to treat diabetes safely.	[178]
Calcium ion cross-linked maltose/alginate microneedle	20	>80	8	Used to encapsulate insulin and diabetes treatment by transdermal ingestion.	[179]
Poly(vinyl pyrrolidone) and insulin-loaded $CaCO_3$ microparticles	5	82	12	High efficiency. Constant release of insulin.	[180]
Modified alginate and hyaluronate microneedle	10	48.4	12	Effective hypoglycemic effect.	[181]
Double-layered bullet-shaped microneedle arrays together with water-swellable tips	10	60	12	Reliable and enhanced adherence to animal skin. Longer than normal insulin release without a blast.	[182]
Gelatin and calcium sulfate microneedle patches with high aspect-ratio microneedles	20	23	12	The released insulin exhibits an effective and obvious hypoglycemic effect for longer time.	[181]

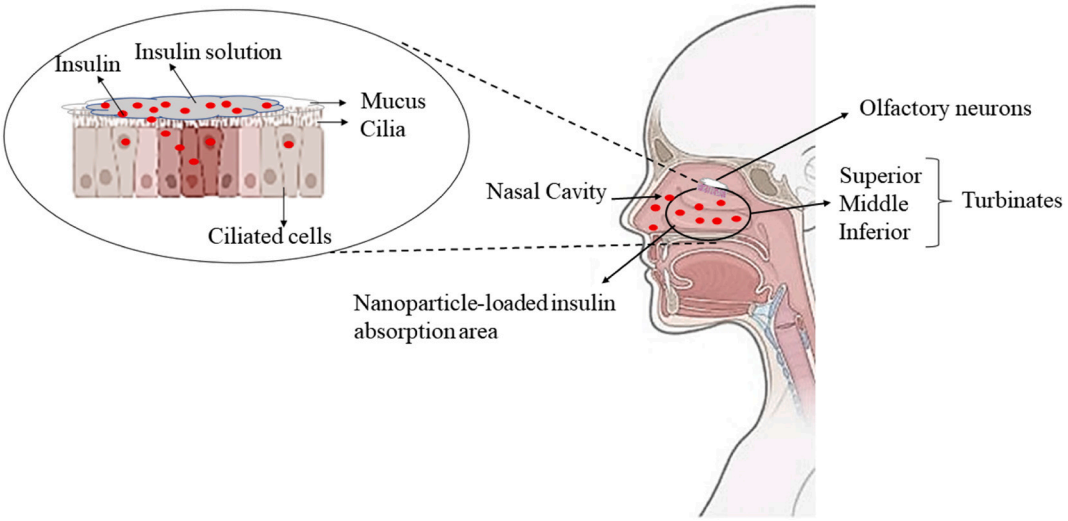

Fig. 5. Nasal insulin delivery methods.

required for biological devices [189]. These hydrogels are non-toxic, soft, and flexible. However, they are unstable (uncontrolled dissolution can occur), have low mechanical strength, and are difficult to control pore size [189]. This polymer is therefore very attractive for biomedical applications, especially in tissue engineering.

The main application area of bio-adhesive gels is in mucous tissues [190]. Because the mucous membrane of the nasal cavity has well-developed blood vessels, this is the preferred site for drug delivery to avoid initial infusion effect and expect the systemic effects, such as desmoprecin acetate for central therapy, diabetes insipidus bucerelin acetate and nafarerin acetate for uterus intima disease [191]. The nasal structure is very complex. The surface area is large, but the drug is delivered rapidly down the throat by biliary muscle movement. Thus, if a drug has poor absorption characteristics, a mucoadhesive that allows the drug to remain in the cavity would be beneficial [191].

Polymeric nature of starch can be used to create microspheres. Because starch is biodegradable, it has been used as a drug excipient for a long time. Using starch microspheres, insulin has been delivered through nasally, orally, and intramuscularly [192]. Starch microspheres have a clearance half-life of around 240 min [192]. Starch nanoparticles are also used for transnasal insulin delivery due to its higher external region, which protects the heavily vascularised nasal absorptive area. Starch nanoparticles for insulin loading were prepared by adopting several approaches with diverse crosslinkers [193]. Starch microspheres are degraded by the involvement of amylase for the release of insulin, which are further exposed by proteases present in the body. Microspherilization is the process of breaking down starch into smaller fragments using high-intensity ultrasound. This method arranges these fragments in a microsphere structure using the same kind of bonds as regular starch [61].

Bio-adhesive systems based on microspheres are developed to fabricate systemic absorption of traditional polypeptides and drugs through the nasal mucosa, local distribution to a specific region, intimate contact with mucosal epithelium, and longer residence time at the site of operation, without using the absorption enhancing agents [194]. Nasal insulin delivery using chitosan solution shows an advanced transmucosal fluidity with a successful enhancement of absorption via nasal mucosa [195]. As a result, the absorption of insulin through the nasal route from chitosan gel as a bio-adhesive polymer raises the enzyme inhibitors and residence time in the nasal cavity and shield the enzymatic degradation of insulin. Nasal insulin bioavailability can be improved by the application of absorption enhancers. For instance, chitosan gel with ethylenediaminetetraacetic acid for nasal delivery of insulin could be replaced for the parenteral pathway [196].

Table 3 presents a summary of data about nasal insulin delivery methods using different polymeric carriers. The nasal insulin delivery was successful for the insulin concentration of 5 and 50 IU/kg in two different studies. The time and percentage release were varied in the

Table 3
Summary of nasal insulin delivery methods in various studies.

Insulin carrier	Insulin concentration (IU/kg)	Insulin release (%)	Duration of release (h)	Remarks	Ref
Chitosan and ionic liquids/deep eutectic solvent	5	76.71 ± 3.49	6	Excellent control of blood glucose levels. A sustained serum insulin profile over the period of several hours.	[44]
Malic acid and choline chloride/deep eutectic solvents	25	<50	48	The in vitro studies demonstrated that this solvent was able to release drugs by erosion caused by the absorption of water.	[197]
Poly(acrylic acid) and poly(vinyl pyrrolidone) interpolymer complexation	10	52.3 ± 18.9	24	Safe multi-unit nasal insulin system.	[198]
β-Cyclodextrin functionalized hyperbranched polyglycerol	5	40	1.5	The insulin-loaded nanoparticles were able to deliver across the nasal captivation. Enhancement in nasal insulin absorption. Decrease in blood glucose concentrations.	[199]
W/O microemulsion	18	75	2	An optimum additional dosing of insulin could be clinically feasible using microemulsions.	[200]
Poloxamer-chitosan/glutaraldehyde/glycine gels	10	60	24	Highly prolonged hyperglycemic effect and improved pharmacological efficiency.	[201]
Polyethylene glycol-grafted chitosan nanoparticles	28	80	24	This type of nanoparticles enhanced remarkably in nasal absorption of insulin.	[202]
Aminated gelatin microspheres	50	54.3%	8 h	Significant hypoglycemic effect. The mucoadhesive properties of the microspheres affect the whole absorption increasing result.	[203]

range of 1.5–48 h with a maximum 80% release for the polyethylene glycol-grafted chitosan nanoparticles.

5.4. Ocular

Ocular delivery is a well-known systemic drug absorption method, even though the conjunctival sac exhibits some absorption [204]. Due to the physiology and anatomy of the eye as a complex and sensitive medium, the ocular route has been known as great approachable macromolecule delivery method (Fig. 6) [205]. Controlled drug delivery systems are also necessary to accomplish an ideal pharmaceutical intervention for insulin delivery through the ocular mode. Biomaterials with polymeric properties perform an essential task in the controlled release of ocular drug delivery into the human body [30]. There are different types of carriers which are applied for ocular insulin delivery. The most common carriers are listed as follows.

Gelfoam is a medical device intended to be applied to bleeding surfaces as a hemostatic agent [206]. Gelfoam sponge (absorbable gelatin sponge) is used in surgical procedures as a hemostatic device when controlling capillary, venous bleeding, and arterioles by pressure, ligation, and conventional procedures are ineffective [207]. No dressing treatment is required and it may be placed directly over an open wound and/or a vessel to stop bleeding [208].

Micro-hydrogel is a submicron- or micron-sized network of polymeric particles that are insoluble in water but highly swellable [209]. Micro-hydrogels have a high-water holding capacity and are sensitive to environmental conditions. Changes in the water content of micro-hydrogels alter their hydrophilicity, size, and surface potential, among other factors [210]. These changes in a microgel can be used to measure its environmental conditions. Therefore, micro-hydrogels can be used for a variety of physicochemical, optical/photonic, biological/biomedical, and chemical applications [209].

The biocompatible micro-hydrogels create fine systems for self-control insulin delivery [211]. Yin et al. [83] prepared dual-responsive Con A-based micro-hydrogels, sensitive to either pH or glucose for insulin delivery. Sensitivity of insulin released from micro-hydrogels is detected when there is a slight variation in pH readings, which immediately improves insulin release due to ionization of amino units and system swelling. Increasing pH causes hydrogen bonding in the amino groups, which further creates a matrix that limits the locomotion in the chains of the polymer network and controls the liberation of insulin [169,170].

Zakharchenko et al. [171] reported insulin-loaded microparticles-based transporter. This bilayer microtube is made of a poly(N-isopropylacrylamide-co-4-acryloyl benzophenone) copolymer, which is a combination of photoresponsive photocrosslinker, thermoresponsive poly(N-isopropyl acrylamide), and hydrophobic polycaprolactone with 4-acryloyl benzophenone. Magnetic nanoparticles mixed with PCL

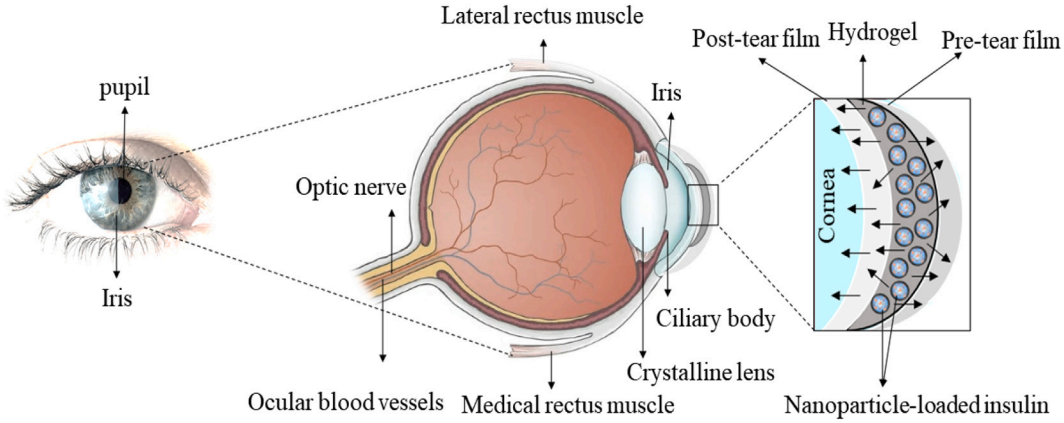

Fig. 6. Ocular insulin delivery methods.

forms the outer layer of the microtube. The bilayer film encapsulates and folds the insulin-loaded microparticles at low temperature (28 °C), while at higher temperature (more than 28 °C) it expands for the release of insulin-loaded microparticles. Magnetic nanoparticles allow self-control of the microtubes using magnetic spheres, which provides a multi-stimuli responsive system [166,171].

Table 4 presents a summary of data about ocular insulin delivery methods using different polymeric carriers. According to the reported studies, insulin delivery via ocular is applicable in concentration 10–50 IU/kg in 1.5–12 h with a maximum release of 87%. In addition, this delivery method relied on gelfoam disc and prolonged insulin activity due to the constant release of insulin caused constant tear production and slow lachrymal systems.

5.5. Rectal

An adult human's rectum is 12–15 cm in length with an average surface area 200–400 cm^2 and a pH in between 7.2 and 7.4 [216]. Rectal delivery method uses rectum as the route for medication and other fluids, which are subsequently absorbed by the rectum's blood vessels (Fig. 7) and flow into the body's circulatory system. This system can be adopted for the distribution of insulin to the various organs of body and other systems [217]. However, the mucous forms a 100 mm coating that protects the rectal epithelia and also acts as a barrier to drug absorption [216]. The superficial vein enters vortex circulation from the upper rectum, whereas the central and inferior veins enter venous blood circulation exclusively from the lower rectum [218]. The rectal system can be considered an effective route for the systemic drug delivery as porto-systemic shunting and lymphatic drainage of the rectum play a significant role in systemic absorption of lipophilic drugs [219]. There are different types of carriers which are applied for rectal insulin delivery. The most common carriers are listed as follows.

N-trimethyl chitosan chloride (TMC) is a polycation that improves drug transport across the epithelium by opening tight junctions [218,219]. Polymers such as chitosan and TMC appear to be mucoadhesive. TMC as a quaternary derivative of chitosan with higher water solubility, can be synthesized by methylation of the amine groups at the C-2 position of chitosan upon reaction with methyl iodide when a strong base exists [220]. TMC can improve the absorption of hydrophilic and macromolecular drugs across the mucosal epithelium. TMC is also effective in neutral media, where chitosan salts precipitate from solution, rendering them ineffective as absorption enhancers at neutral pH values. The charge density of TMC plays an important role in the absorption enhancing properties of this polymer, especially in neutral and alkaline media [221].

Poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) triblock copolymers (PEO–PPO–PEO), known as Pluronic®, has surfactant properties and is widely used in pharmaceutical systems [222]. The Pluronic hydrogels exhibit significant viscosity, partial stiffness, and a specified persistence time, due to the ordered micellar packing structure and intermuscular entanglements. The above properties facilitate the combination of both hydrophobic and hydrophilic drugs [223]. In addition, some concentrated aqueous solutions of Pluronic exist in a sol state at room temperature but form gels at physiological temperatures. Therefore, Pluronics are widely used in the injectable in situ drug delivery matrices. Compared with solutions, Pluronic hydrogel can prolong drug release time [224]. However, there are still many disadvantages in the Pluronic hydrogel system, such as low mechanical strength, short residence time, high permeability, non-biodegradation, and limitations on molecular weight. Because these disadvantages of Pluronics limit their application in advanced drug delivery systems, Pluronics has recently been improved. Several oligomers of Pluronic F127 were prepared by splicing F127 monomers using hexamethylene diisocyanate or phosgene as coupling reagents [134].

PF127 is a block copolymer comprising of poly(oxypropylene) and poly(oxyethylene) sections. The gelation property of PF127 aqueous solution in the 20–35% concentration range was used as an ophthalmic drug delivery system [225]. Rectal insulin absorption is caused by all PF127 gels [226]. One essential property of PF127 gel is the improvement of the constancy of loaded proteins in the gel composite with their full recovery when the gel is dispersed in an extra buffer. Moreover, the PF127 gel can deliver rectally as a rigid semisolid gel network that warms at 37 °C in the body [225].

Chitosan, its glutamate, and hydrochloride salts retain enhanced absorption characteristics, and have been recognized for their various applications in the past few years [227]. Oligomers of chitosan have been explored for insulin intestinal absorption. The absorption of insulin in the jejunum increased due to the presence of hexamers of chitosan. As chitosan is not a strong base, the conversion of the glucosamine units into positively charged species needs a volume of acid. *N*-trimethyl chitosan chloride, a chitosan derivative in different levels of trimethylation can increase the delivery of insulin in Caco-2 cell monolayers [156,182,183]. *N*-trimethyl chitosan chloride can enhance the allowance of cationic and neutral peptide thru Caco-2 intestinal epithelia. It also can become active at neutral and basic pH [228]. The absorption of insulin through mucosal epithelia can be increased using such polymers. This is due to the fixed negative charges in the strong bonds and activation of the reversible breaking of the strong bonds [228].

Table 5 summarizes reports on rectal insulin delivery methods using different polymeric carriers. As shown in Table 5, the concentrations of insulin delivery using the rectal method was varied between 5 and 20 IU/kg with 24–48 h and 75.9% release efficiency. Besides, insulin carrier in this route was related to multiple emulsions of eicosapentaenoic acid, oleic acid, and docosahexaenoic acid. In addition, in rectal delivery, docosahexaenoic acid improved insulin permeability with low toxicity, which acts as an absorption enhancer for insulin transmission through the intestine.

Table 4
Summary of ocular insulin delivery methods in various studies.

Insulin carrier	Insulin concentration (IU/kg)	Insulin release (%)	Duration of release (h)	Remarks	Ref
Gelfoam disc	20	80	12	With the Gelfoam device, it is possible to achieve a prolonged systemic delivery of insulin while maintaining therapeutic levels without the risk of hypoglycemia.	[212]
Modified *Quillaja* saponin	50	75	1.5	The improved saponin was effective at developing ocular insulin delivery at extremely low concentrations.	[213]
Gelfoam disc	28.6	87	6	The lengthy insulin activity is caused by the constant insulin release from the device that results from the constant tear production and slow lachrymal systems.	[214]
Gelfoam + sodium/zinc insulin + diluted acetic/hydrochloric acid	20	60	8	Insulin may be delivered into the bloodstream without the need of a chelating agent or a surfactant to assist in adsorption.	[207]
Quillaja saponins	10	>60	2	Deacylated saponin represents an interesting candidate for inclusion in formulations designed to improve ocular insulin delivery.	[215]

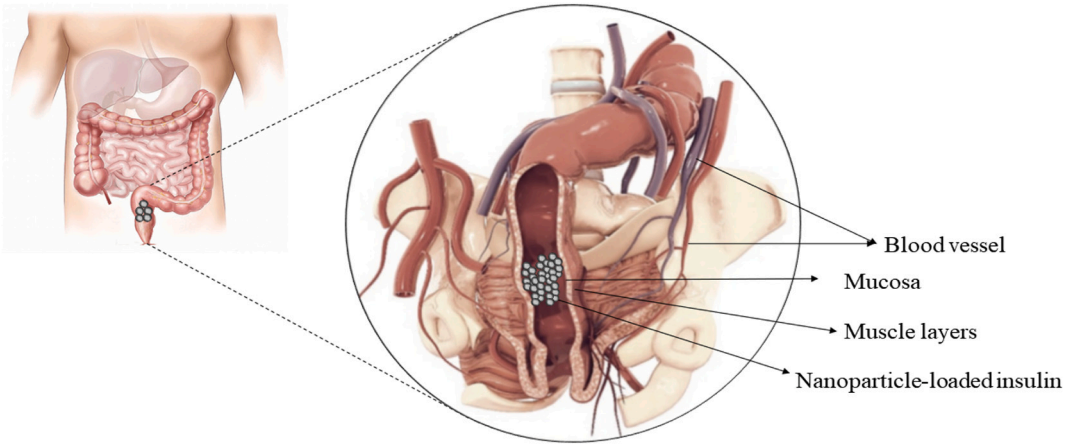

Fig. 7. Rectal insulin delivery methods.

Table 5
Summary of rectal insulin delivery methods in various studies.

Insulin carrier	Insulin concentration (IU/kKg)	Insulin release (%)	Duration of release (h)	Remarks	Ref
Hydroxypropyl methyl cellulose-co-polyacrylamide-co-methacrylic acid	20	72.6 ± 6.1	24	Efficient hypoglycemic impact. This approach has the potential to increase diabetic patients' conformity.	[217]
Methylcellulose and polyacrylate binary hydrogels	20	67.2 ± 3.9	25	Efficient hypoglycemic impact. This approach has the potential to increase diabetic patients' conformity.	[219]
W/O/W multiple emulsion of oleic acid, eicosapentaenoic acid, and docosahexaenoic acid	5	75.9	48	Insulin permeability is enhanced by docosahexaenoic acid. Toxicity is minimal. Insulin transport into the intestine is aided by this absorption enhancer.	[224]

5.6. Vaginal

Another potential route for drug delivery is through vaginal systemic. The vagina is a fibro-muscular conduit about 10 cm long (Fig. 8). The vaginal wall is well adapted for drug absorption for systemic application due to the dense network of blood vessels. The vagina is exceptional as it comes to menstrual secretion, enzyme activity, pH, and microflora. Both variables influence the formulation spreading and retention, absorption, and drug release in the vagina. The use of a permeation enhancer and a PAA aqueous gel can improve the bioavailability of vaginally administered peptides significantly. The poor absorption through the vaginal epithelium occurs normally due to the degradation by vaginal lumen enzymes which causes lower bioavailability of proteins and peptides after vaginal delivery [229]. There are different types of carriers which are applied for vaginal insulin delivery. The most common carriers are listed as follows.

Niosome (vesicles containing non-ionic surfactants obtained by hydration) is microscopic lamellar structures formed by combining a non-ionic surfactant from an alkyl ether or dialkyl polyglycerol ether class with cholesterol [230]. In the bilayer structure, the hydrophobic parts are oriented away from the aqueous solvent, while the hydrophilic ends remain in contact with the aqueous solvent. Due to presence of hydrophilic, amphiphilic, and lipophilic segments in the structure, they can contain drug molecules with wide solubility [231]. These can act as a depot, releasing the drug in a controlled manner. Therapeutic efficacy of drug molecules can also be improved by delaying clearance from the circulation, protecting the drug from the biological environment, and limiting effects on target cells. It can also be used as a vehicle for poorly absorbed drugs to design new drug delivery systems [230]. It improves bioavailability by crossing the anatomical barrier of the GI tract through

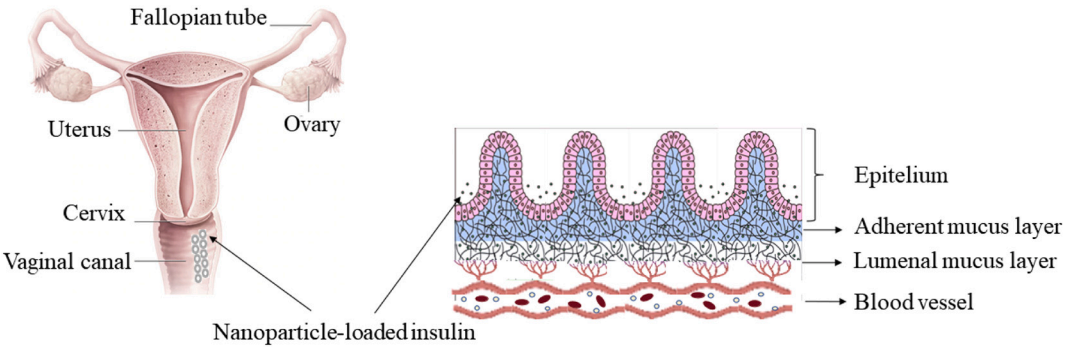

Fig. 8. Vaginal insulin delivery methods.

M-cells transformation of Peyer's patches in intestinal lymphatic tissues. The vesicles are permeable to oxygen and haemoglobin dissociation curve can be altered to resemble unencapsulated hemoglobin. Its vesicular system also allows for better drug concentration at the site of action by oral, parenteral, and topical administration [232]. The sustained release activity of niosome can be applied to drugs with low therapeutic index and low water solubility. Administration of drugs via niosome is one of the approaches to achieve localized effects of drugs given their size and low ability to penetrate through the epithelium and connective tissue, keeping the drug localized at the site of administration. Localized drug action improves the effectiveness of the drug's potency and at the same time reduces its systemic toxic effects, e.g., in terms of dose and toxicity [230].

Microspheres play an important role in improving the bioavailability of common drugs and minimizing side effects [233]. The main advantage of adopting microspheres as a drug delivery system is controlled drug release. Microencapsulation has been used to delaying the release of drugs from dosage forms and reducing side effects, thereby increasing the patient compliance. Microspheres provide a long-lasting and continuous treatment effect [234]. Reduction of particle size improves the solubility of poorly soluble drugs [235]. Microspheres protect drug from enzymatic and photolytic cleavage and therefore was found to be the best for protein delivery. They provide controlled, sustained, and targeted drug delivery. Biodegradable microspheres have an advantage over large polymer implants in that they do not require surgical intervention for implantation and removal [236]. Microspheres create a more reproducible drug absorption capacity. Flow of the drug into stomach is impeded and thus local side effects are reduced. Using microspheres, a better therapeutic effect can be obtained in the short half-life of the drug [228]. Microspheres help avoid drug-recipient's incompatibilities especially with buffers. Microspheres avoid the first-pass metabolism and can be injected into the body easily due to their small spherical size. They improve biological half-life and bioavailability. Controlled release with biodegradable microspheres is used to control drug release rates, thereby reducing toxic side effects, and eliminating the inconvenience of repeated injections. Microspheres also reduce the risk of GI irritation [237].

The aqueous gel basis of PAA has the capability of continuous release enhancement to accomplish extended time of hypoglycaemia [174]. In diabetic rabbits and rats, suspended insulin in the PAA gel base was used to increase the percentage of vaginal absorption for systemic transmission. As insulin is administered via the vagina in the preparation of gel insulin suspension, plasma insulin reaches a plateau, and hypoglycemic effects were controlled (0.1%, pH 6.5) to rabbits and rats. Further, the plasma insulin rapidly reduced after 1 h and returned to normal after 3 h [238].

Encapsulating insulin in liposomes, niosomes, and microspheres has been developed for protecting it from enzymatic degradation in the absorption route. Niosomes (non-ionic surfactant vesicles) have achieved much consideration in the recent past for their superiority in therapeutic effectiveness, reduction of toxicity, biodegradability, and absorption enhancement. Besides, their chemical properties are more constant compared to liposomes. Hence, niosomes are extensively utilized as a drug carrier for protein and peptide. Via vaginal insulin distribution, insulin-Span 40 and 60 niosomes has an appealing impact. After encapsulation of insulin in niosomes, it becomes a powerful and energetic medicinal agent [28,186].

In sheep, insulin was administered vaginally as a lyophilized powder and as an aqueous solution contained inside bio-adhesive starch microspheres [235]. The effect of lysophosphatidylcholine was measured using insulin vaginal absorption from both preparations in sheep. The results showed minimal vaginal absorption of insulin from solution. However, the addition of lysophosphatidylcholine caused an increase in insulin and a decrease in plasma glucose [235].

Table 6 presents a summary of data about vaginal insulin delivery methods using different polymeric carriers. The vaginal method was effective in insulin concentration between 1 and 5 IU/kg. Based on the finding from different studies, the time of release was varied between 3 and 24 h with 98% of maximum release for the freeze-dried cylinders carrying chitosan nanoparticles as insulin carrier. In addition, these freeze-dried cylinders can incorporate and release chitosan ascorbate and insulin-loaded nanoparticles into the vaginal atmosphere while retaining their polydispersion index, morphology, and size.

6. Comparison of different insulin delivery methods

To achieve the ideal insulin delivery, different materials have been developed as drug carriers with different abilities. These carriers, including organic and inorganic materials, are successfully employed for potential delivery of insulin through various routes. Therefore, from the results (Tables 1 to 6), it can be concluded that chitosan is one of the best drug carriers for insulin delivery. Drug delivery procedure makes various carriers to carry a certain amount of drug for passage through the epidermal layer of the mucosa or skin to enter the systemic blood vessel at a controlled rate. The advantages and limitation of each route have been highlighted in Table 7.

7. Conclusion and future prospective

The present review summarizes the biomedical application of polymers with an emphasis on insulin delivery via different routes. Among the different methods and periods of insulin release along with their advantages and disadvantages, it can be concluded that the transdermal delivery method has several disadvantages in terms of low permeability though the skin, poor dose accuracy, and difficulties in conveyance, but the efficiency of the transdermal insulin delivery has been the highest

Table 6
Summary of vaginal insulin delivery methods.

Insulin carrier	Insulin concentration (IU/kg)	Insulin release (%)	Duration of release (h)	Remarks	Ref
Niosome Span 60	3	27	24	Insulin is an active therapeutic agent after being encapsulated in niosomes. A suitable carrier for protein drug delivery via vaginal route.	[229]
Lysophosphatidyl choline and a bioadhesive microsphere delivery system	2	32.5	6	The vaginal absorption of insulin was greatest in combination with lysophosphatidyl choline formulations. Ease of administration needs to be considered for routine vaginal drug delivery.	[239]
Polyacrylic acid aqueous gel	1	15	5	The findings suggest that vaginal administration of insulin gel preparations could be useful as a quick and painless dosage type in the long-term treatment of diabetes.	[240]
Freeze-dried cylinders carrying chitosan nanoparticles	5	98	3	These freeze-dried cylinders will incorporate and release chitosan ascorbate and insulin-loaded nanoparticles into the vaginal atmosphere with no discernible changes in morphology, size, or polydispersion index.	[241]

Table 7
Advantages and disadvantages of different types of non-invasive route in insulin delivery.

Types of delivery route	Advantages	Disadvantages
Oral	1. Large surface area 2. Patient compliance 3. Inexpensive production 4. Most acceptable by patients 5. Efficacious in achieving euglycemia 6. Best mimics normal insulin release by the pancreatic islets of Langerhans 7. Insulin absorbed by the gastrointestinal tract may be delivered directly to the liver. 8. Painless and simpler than traditional injection technologies	1. Thin alveolar epithelium 2. Rapid protein/peptide absorption 3. Low bioavailability via non-parenteral routes 4. Short half-life in vivo 5. The intestinal epithelium serves as a significant permeability buffer, and the hepatic first pass effect is attributable to the acidic pH and enzymatic cleavage of protein drugs. 6. Fat deposits, hyperinsulinemia, and local hypertrophy at injection sites 7. The liver receives just about 20% of insulin. 8. Fast degradation by elastase, trypsin, and α-chymotrypsin to a lesser degree by other enzymes found at the GI brush-border membranes 9. Unpredictable/low bioavailability 10. Limiting protein delivery 11. Poor penetration of the proteins across mucosal or skin barriers 12. Variable inhalation efficiency
Vaginal	1. The surface area is large. 2. Blood supply is rich. 3. Peptide and protein permeability 4. Treatment of female-related conditions 5. Rich vasculature 6. Useful in pediatric and geriatric patients 7. Painless 8. Simpler than traditional injection 9. Hepatic first-pass metabolism is avoided. 10. Gastrointestinal side effects are reduced. 11. Drugs like steroids have less hepatic side effects. 12. Overcoming tissue injury 13. Overcoming of the possible infection was found using parental paths.	1. Inadequate absorption through the vaginal epithelium 2. Degradation of peptides and proteins by enzymes in the vaginal lumen 3. Inadequate bioavailability after vaginal delivery 4. Unpredictable/low bioavailability 5. Limiting protein delivery 6. Poor penetration of the proteins across mucosal barriers 7. Variable inhalation efficiency
Rectal	1. Rich vasculature 2. Useful in pediatric and geriatric patients 3. Painless 4. Simpler than traditional injection technologies	1. About two-thirds of the insulin ingested from the rectum enters the general circulation. 2. Poor and erratic insulin absorption from the rectum 3. Unpredictable/low bioavailability 4. Limiting protein delivery 5. Poor penetration of the proteins across mucosal barriers 6. Variable inhalation efficiency
Ocular	1. Easily accessible targets 2. Fast rate of systemic absorption 3. Immunological responses are less sensitive. 4. It avoids gastrointestinal and liver side effects. 5. After three months of occasional insulin eye drops, there were no negative side effects.	1. Low bioavailability of insulin 2. Rapidly cleared off 3. Short retention time 4. Need for frequent dosing 5. Ultimately dose-dependent side effects 6. Low patient compliance 7. Long extended-release profile 8. Tear turnover is fast. 9. Reflex blinking and nasolacrimal draining 10. Less penetration of insulin 11. Poor drug uptake 12. No specificity to target tissues 13. Systemic side effects 14. Poor adherence to therapy
Nasal	1. Rich vasculature 2. Useful in pediatric and geriatric patients 3. Avoids the disadvantages of injections 4. Rapid insulin absorption 5. Avoidance of gastrointestinal and hepatic metabolism 6. Painless 7. Simpler than traditional injection 8. Low local proteolytic activity 9. Easy to elicit strong immune responses 10. Requires lower doses of insulin 11. Bypassing first pass metabolism by the liver 12. Insulin absorption is aided by a large surface region. 13. Highly vascularized subepithelial layer 14. Preventing hepatic first pass metabolism 15. Achieving a therapeutic blood level in a short period of time 16. Pharmacological activity begins more quickly. 17. Side effects are reduced.	1. Poor permeability across the nasal mucosa 2. Unpredictable/low bioavailability 3. Limiting protein delivery 4. Poor penetration of the proteins across mucosal barriers 5. Variable inhalation efficiency 6. Poor permeability across lipophilic membranes 7. Poor permeability via the paracellular route 8. The mucociliary clearance mechanism
Transdermal	1. Good patient compliance 2. Possibility of controlled release over time 3. Possibility to attain sustained and constant insulin levels 4. Avoiding possible drug degradation 5. Patients may obtain subcutaneous insulin without the use of a needle using jet injector systems.	1. Low permeability of the skin 2. Patients who are afraid of injection pain face a challenge. 3. Poor patient compliance 4. Increased probability of infections 5. Weak dose accuracy 6. Prolonged treatment duration 7. Irritating psychologic impact 8. Difficulties in conveyance 9. Jet injectors are rather expensive, cumbersome, and there are some infection problems.

Source: [42,43,205,218,229,242-262].

among all the routes.

Moreover, the unexpected side effects of these novel studies must be taken into consideration for designing efficient delivery system. Although much research has been carried out to develop successful insulin delivery systems, some scientific tasks have also needed greater attention. Future development in insulin delivery includes incorporation of prolonged release and reduction of probable side effects of each delivery route. It is also possible to fabricate glucose-sensitive multi polymer composites to start the release of insulin in case of any glucose reduction in the body. Conversely, the use of toxic chemicals/polymers in preparation of insulin carriers can be replaced with green solvents to avoid the negative impact. It is necessary to evaluate various toxicological studies before fabrications of carrier.

Declaration of competing interest

All authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

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