ISSN: 2755-1067

Journal of Diseases Disorders & Treatments

SCIENTIFIC Research and Community

Review Article

Open Access

Comparative Advances in Natural and Synthetic Polymer based Drug Delivery Systems for Diabetes Mellitus

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ABSTRACT

Background: Diabetes affects approximately 537 million people worldwide. As such, there is a growing need for treatment options that go beyond pharmacotherapy alone. Drug delivery systems (DDS) made from polymers have been developed to address some of the challenges commonly associated with drug delivery, including low bioavailability, inconsistent absorption rates, and high frequency of administration.

Objective: The purpose of this review is to compare natural polymers (i.e., chitosan, alginate, gelatin, hyaluronic acid, and dextran) to synthetic polymers (i.e., PLGA, PEG, PLA, PCL, and dendrimers) when used for insulin delivery, encapsulation of oral hypoglycaemic drugs, and glucose-responsive formulations.

Methods: The literature was searched using PubMed, Scopus, and Web of Science databases for articles published between 2010 and 2025, yielding numerous relevant articles.

Results: Natural polymers exhibit greater biocompatibility and mucoadhesion than synthetic polymers; however, they are limited by variability between batches and heterogeneity in structure. Conversely, synthetic polymers typically contain tunable degradation profiles and reproducibility as well as stimulus-responsiveness. Concerns associated with synthetic polymers include immunogenicity, and complexity of preparation. Hybrid formulations that contain both natural and synthetic polymers exhibit synergistic benefits and reduce the HbA1c by 1.4% to 2.5%.

Conclusion: Continued innovation in the development of smart, glucose-responsive, and personalised polymer-based DDS has the potential to revolutionise the treatment of diabetes. Additionally, regulatory alignment and strategies for scaling up manufacturing processes were identified as critical priorities.

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Received: May 11, 2026; **Accepted:** May 16, 2026; **Published:** May 25, 2026

Keywords: Diabetes Mellitus, Polymer-Based Drug Delivery Systems, Natural and Synthetic Polymers

List of Abbreviations
AI: Artificial Intelligence
CGM: Continuous Glucose Monitor
Con A: Concanavalin A
DDS: Drug Delivery System
DM: Diabetes Mellitus
EV: Extracellular Vesicle
FDA: Food and Drug Administration
GelMA: Methacrylated Gelatin
GLP-1: Glucagon-Like Peptide-1
GMP: Good Manufacturing Practice
GOx: Glucose Oxidase
GR: Glucose-Responsive
HA: Hyaluronic Acid
HbA1c: Glycated Haemoglobin A1c
IDF: International Diabetes Federation
LADA: Latent Autoimmune Diabetes in Adults
ML: Machine Learning
MN: Microneedle
NPs: Nanoparticles
PAMAM: Polyamidoamine
PBA: Phenylboronic Acid
PCL: Polycaprolactone
PDI: Polydispersity Index
PEG: Polyethylene Glycol
PLA: Polylactic Acid
PLGA: Poly(lactic-co-glycolic acid)
PVA: Polyvinyl Alcohol
RGD: Arginine-Glycine-Aspartate
SC: Subcutaneous
T1DM: Type 1 Diabetes Mellitus
T2DM: Type 2 Diabetes Mellitus
TPP: Tripolyphosphate.

Introduction

Diabetes Mellitus (DM) is a long-term ailment characterised by high blood sugar levels due to either lack of production from the pancreas or inability of the body to effectively use the insulin produced. The International Diabetes Federation (IDF) estimates there are 537 million individuals between the ages of 20 to 79 years diagnosed with diabetes in 2021 and this number is predicted to increase to 783 million by 2045 [1,2]. Type 1 Diabetes (T1D) results from autoimmune destruction of the pancreatic beta cells

thus requiring insulin therapy. Type 2 Diabetes (T2D) accounts for about 90% of the diabetic population and is a result of insulin resistance combined with exhaustion of the beta-cells. Other clinical forms of diabetes that exist include gestational diabetes, Latent Autoimmune Diabetes in Adults (LADA), and monogenic forms of diabetes; these have expanded the spectrum of conditions that are diagnosed as diabetes [3,4].

Standard treatment options for the management of diabetes include exogenous insulin (i.e., insulin analogues), biguanides (i.e., metformin), sulphonylureas, thiazolidinedione, glucagon-like peptide-1 receptor agonists (i.e., GLP-1 receptor agonists), sodium-glucose co-transporter 2 (i.e., SGLT-2) inhibitors, and dipeptidyl peptidase-4 (i.e., DPP-4) inhibitors. As a result of the limited range of acceptable glycaemic control in a large percentage of people living with diabetes, the major factors defer in obtaining adequate control are non-compliance by patients, inconsistent bioavailability of orally administered peptide drugs, and narrow therapeutic windows [5,6].

Polymer-based drug delivery systems (DDS) are transforming how diabetes is treated by allowing a more precise, focused and reactive way of administering medication. Therapeutic agents are placed inside the polymer (from either natural or synthetic origins), thus enabling the extended residence time of the drug, protecting Frontline Drugs (such as insulin) from being broken down by enzymes, and allowing for special targeting of specific organs for treatment purposes [7,8]. The polymer technology has evolved beyond simple polymer chains to include advanced formulations such as stimuli-responsive (or "smart") hydrogels, surface-modified nanoparticles, liposomes, dendrimers, and hybrid systems. The primary driver of these advances has been the understanding of the physics and chemistry of polymers, biocompatibility and biodegradability of materials, and biological-material interactions [9,10]. This article presents a comprehensive comparison of the capabilities and limitations of both natural and synthetic polymer platforms for delivering diabetes medications. Specifically, an in-depth analysis is provided on the physicochemical characteristics, mechanisms of drug release, relevant animal models, and potential applications in humans, of both natural and synthetic polymer platforms. In conclusion, we wanted to provide a helpful reference to researchers, physicians, and pharmaceutical scientists who are developing and testing novel diabetes therapies [11,12].

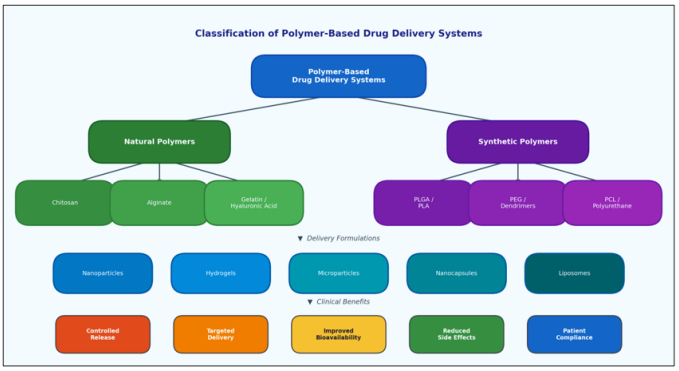

Figure 1: Hierarchical Classification of Natural and Synthetic Polymer-Based Drug Delivery Systems with Clinical Benefits in Diabetes Mellitus

Natural Polymer-Based Drug Delivery Systems

Chitosan

Chitosan, which is a deacetylated version of chitin and is sourced from the hard shells of crustaceans, has been studied the most in terms of being a potential natural polymer for delivering DM drugs. The cationic nature of chitosan at near neutral physiological pH allows it to form electrostatic interactions with the negatively charged mucosal surfaces. This creates powerful mucoadhesive properties with chitosan, which prolongs the amount of time that it remains in the gastrointestinal tract (GI) and enhances the paracellular permeation of some macromolecular drugs such as insulin [13,14]. Chitosan nanoparticles (NPs) made using ionic gelation with tripolyphosphate (TPP) have been shown to have oral bioavailabilities for insulin between 4.8 and 14.9% in animal models, while unprotected insulin has been shown to have less than 1% bioavailability and this increased bioavailability of insulin is most likely due to the endosomal escape caused by the proton sponge effect [15,16]. Chitosan-zinc insulin complexes have been encapsulated inside pH-sensitive Eudragit S100 microparticles and have been able to sustain normoglycaemia for six hours when administered orally to streptozotocin-induced diabetic rats. The absolute bioavailability of these insulin complexes was 11.3% which is a breakthrough event in the field of oral insulin delivery [17].

Alginate

Sodium alginate is a linear chain of repeating units of sodium and is found in the cell walls of brown algae. When sodium alginate is cross-linked with divalent cations such as Ca2+ or Ba2+, it forms stable hydrogel beads that are useful for encapsulating cells for therapeutic applications, such as providing a site in which to implant insulin-producing cells in order to facilitate an "immune-privileged" transplant of pancreas islet cells [18,19]. Clinical trials of encapsulated human islets, developed using alginate hydrogel beads produced by Living Cell Technologies, have demonstrated that the use of implanted encapsulated human islets can result in insulin independence for up to 14 months in some T1DM patients. In addition, patients required an average of 37% less exogenous insulin during this time period than they did before receiving the encapsulated human islets. Alginate formulations containing high-G (guluronate-rich) have greater mechanical rigidity, and lower levels of pericapsular fibrosis, than do formulations containing high-M (mannuronate-rich) alginate [20,21].

A combination of chitosan-alginate composite capsules made by Sarmento et al. have been demonstrated to have a significantly greater insulin encapsulation efficiency (89.4 ± 2.3%) and a significantly lower burst release when compared to single polymer systems, as well as have retained biological activity when measured by radio-immunoassay and glucose-stimulated insulin secretion [22].

Gelatin and Hyaluronic Acid

Gelatin is obtained through hydrolysis of collagen and includes RGD sequences that promote cell Attachment to the hydrogels, resulting in enhanced tissue integration/neovascularization. Thus, gelatin is especially useful as an islet transplantation scaffold or wound dressing for diabetic patients. Methacrylated gelatins that have been crosslinked with UV light have been utilized to encapsulate beta-cells while retaining the ability to secrete insulin in response to glucose for 21 days in vitro [23,24]. Hyaluronic Acid (HA)(>gMw) has been used for delivery of ocular drugs to diabetic patients with diabetic retinopathy and for intraarticular delivery of drugs to diabetic patients with diabetic arthropathy. Insulin nanoparticles (NPs) coated with HA were taken up via receptor-mediated mechanisms (i.e., CD44 and RHAMM receptors overexpression associated with inflamed diabetic tissues) delivering insulin to diabetic patients while minimizing off-target delivery of insulin [25,26].

Dextran and other Natural Polymers

Backbone for glucose-sensitive (responsive) insulin delivery systems that use dextran (a bacterial polysaccharide composed predominantly of α-1,6-linked glucose units (subunits)). The hydrogels of dextran/concanavalin A (Con A) bind competitively to both ambient levels of glucose and provide the ability to self-regulate insulin release using Con A-dextran dissociation, like the physiological feedback loop exhibited by the patient's pancreatic beta cells to regulate their own secretion of insulin. The dissociation of Con A-dextran occurs at glucose concentrations ranging from 200 to 400 mg/dL, which results in a proportional amount of insulin being released [27,28]. In addition to dextran and Con A, a number of other polymers that are derived from natural sources, including guar gum, xanthan gum, pectin, and cellulose derivatives, have been evaluated as compression coated oral drug formulations containing DM, mainly for delivering metformin and glibenclamide to the colon, taking advantage of the degradation of these polymers by microorganisms in the caecum to give rise to the release of the active ingredients at the desired site within the gastrointestinal (GI) tract [29,30].

Synthetic Polymer Based Drug Delivery System

PLGA and PLA

PLGA (poly (lactic-co-glycolic acid)) is recognized as being the leading clinically proven biodegradable synthetic polymer and has received FDA approval for a number of sustained-release injectable devices. PLGA's degradation kinetics, from weeks to months, can be adjusted through the lactic:glycolic acid ratio, allowing a tailored drug release profile from a single-dose implant. By WAY OF EXAMPLE, exendin-4 (GLP-1 agonist) has been incorporated into PLGA microspheres, which produced therapeutic plasma levels during Phase III trials [31,32]. The pancreatic uptake of PLGA nanoparticles that had been target-decorated with anti-transferrin receptor antibodies in diabetic mice was found to be 3.2 times greater than that of non-target-decorated controls, demonstrating greater success with beta-cell regeneration. In addition, the development of a hydrolytic acidic microenvironment (lactic and glycolic acid) during the degradation of PLGA leads to the destabilization of acid-labile peptide drugs such as insulin; therefore, buffering agents such as either $Mg(OH)_2$ or $ZnCO_3$ should be added to the formulation [33,34].

PEG and Stealth Nanoparticles

Insulin has undergone an alteration to make it easier to use for people suffering from diabetes. The alteration of insulin by the addition of polyethylene glycol (PEG), called PEGylation, reduces the risk of developing an immune response from using the medication, increases how long it stays in the bloodstream, decreases how fast it gets filtered out by the kidneys, and thereby allows people to take it subcutaneously once every week instead of every day. The PEGylated insulin lispro developed by Eli Lilly, or LY2605541, has shown preferentially acting on the liver and lower risk of causing hypoglycaemia relative to the use of the long-acting insulin; however, Phase III studies using this formulation were discontinued due to increased elevations in liver enzymes [35,36]. In addition, core-shell nanoparticles made from a combination of polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA) produced longer circulatory times (mean of 18.6 hours) than uncleared PLGA (mean of 3.2 hours) and had a 2.1-fold greater pancreatic bioavailability. Also, the density of the PEG brushes significantly affected the adsorption of proteins to the nanoparticles and their subsequent evasion by macrophages [37].

Dendrimers

Dendrimers, which are branched molecules in a structure that produces uniform molecules of consistently sized molecules, contain multiple groups of branches at the end (the branches become known as the terminals). In clinical trials, the combination of PAMAM dendrimers with folate and metformin demonstrated that they can release drugs rapidly when exposed to acid conditions that occur in tumour tissue (6.5–6.8 pH) and therefore potentially could be used to treat diabetes-related cancers in diabetic patients [38,39]. Developed peptide dendrimers that are also equipped with CPPs for the transport of insulin into the brain show promise in preventing the development of Alzheimers in those patients with Type 2 diabetes who are also insulin resistant. Clinical studies indicated that G4 PAMAM dendrimers modified with PEG have low levels of blood-cell toxicity at levels that would be present even if they were not modified to carry drugs (IC_{50} > 500 μg/mL) [40].

PCL Polyurethanes and Emerging Synthetics

Long-Lasting Insulin Delivery Devices Use the Biodegradable Polymer PCL to Create Long-Acting Implants for Glucose Regulation in People with Diabetes, Due to the Slower Rate of Hydrolytic Degradation of PCL (i.e., 2-4 Years), and the Excellent Mechanical Properties of PCL. Studies in Diabetic Rat Models of PCL-Based Insulin Delivery Systems Demonstrate an Extended Period of Normoglycemia from the PCL-based Insulin Delivery Device (90 Days). Zero-order release kinetics were observed during the first 60 days of the PCL-based insulin delivery device, with mechanical support provided by the PCL/chitosan blend. Synergistically, the combination of PCL and chitosan imparts mechanical strength (PCL) and mucoadhesive qualities (chitosan) to create long-term delivery vehicles for insulin [41,42]. Glucose Responsive Shape-memory Polyurethane actuators for Diabetes Mellitus Delivery of Insulin, operate by compressing an Insulin reservoir in Reaction to changes in Blood Glucose, thus providing a closed loop mechanism of delivery without the usage of Enzymatic Catalysts. The non-immunogenic properties of Polymers; Poly(2-oxazoline) are superior to those of Polyethylenglycol and demonstrate improved Thermo-responsive properties for use in transdermal insulin delivery for management of diabetes mellitus [43,44].

Table 1: Comparative Overview of Natural and Synthetic Polymers for Diabetes Drug Delivery

Polymer	Origin	Key Properties	MW (kDa)	Applications in DM	Limitations
Chitosan	Natural (chitin)	Mucoadhesive, cationic, biodegradable	50–2000	Insulin nanoparticles, oral delivery	pH-sensitive solubility
Alginate	Natural (brown algae)	Hydrophilic, biocompatible, gelation	32–400	Islet encapsulation, hydrogels	Poor mechanical strength
Gelatin	Natural (collagen)	Biocompatible, cell-adhesive	15–250	Wound dressings, scaffolds	Rapid degradation
Hyaluronic Acid	Natural (ECM)	Viscoelastic, anti-inflammatory	100–8000	Ocular delivery, intra-articular	Short half-life
Dextran	Natural (bacteria)	Hydrophilic, inert, biocompatible	10–2000	Glucose-responsive systems	Low drug loading
PLGA	Synthetic	Biodegradable, tunable degradation	10–100	Microparticles, implants	Acidic degradation by-products
PEG	Synthetic	Hydrophilic, stealth, non-immunogenic	0.2–40	PEGylated insulin, liposomes	Non-biodegradable
PLA	Synthetic	Biodegradable, crystalline	10–200	Implants, sustained release	Brittle, slow degradation
Dendrimers	Synthetic	Monodisperse, multivalent	3–200	Gene therapy, targeted delivery	Complex synthesis, cytotoxicity
PCL	Synthetic	Semi-crystalline, hydrophobic	10–80	Long-term implants, scaffolds	Slow degradation (2–4 yr)

Advanced Formulation Strategies

Glucose Responsive System

The ultimate alternative to the automatic delivery of insulin is the glucose-responsive drug delivery system (GR DDS) that mimics the way negative feedback is used by pancreatic beta cells. There are three ways of sensing glucose: through the use of an enzyme called glucose oxide (GOx), which can release drugs using either pH or oxygen as triggers; through the use of phenylboronic acid (PBA)-glucose, which has a reversible covalent bond that allows for growing or swelling of the hydrogel would release the drug; and by competing with Con A for binding to the dextran to which the insulin is conjugated [45,46].

Hydrogels made of injectable PLGA-PBA that are loaded with both insulin and GOx released insulin according to the amount of glucose present in the physiological range (~70-400 mg/dL) within 10 minutes in vitro and maintained near-normal blood glucose levels for 6 hours after injection in diabetic mice. Nishiyama et al. created a dual-enzyme (GOx + catalase) system that can scavenge H_2O_2 from reactive oxygen species (ROS), which posed a significant challenge in previous GOx delivery systems due to the potential for cytotoxicity [47,48].

Microneedle Patch Systems

The hyaluronic acid or PVA microneedle patch system creates an efficient way of administering insulin and GLP-1 analogs to the body without using traditional methods like needles or cannulas and allowing insulin and GLP-1 to go through the bloodstream rather than the liver first (the "first pass" effect). Insulin delivered with HA-based MN patches was shown to have a transdermal delivery flux that was 2.8 times greater than that of ETH-based MN patches, and when tested in T1DM mice, it normalized their blood glucose levels within 30 min after administration [49,50].

System with closed-loop interaction between MN deployed under the skin having continuous glucose sensing enzyme and glucose-responsive insulin delivery reservoir (next level). Chen et al. developed a PLGA/HA composite MN with autonomous glucose sensing and self-regulating insulin delivery that maintained 85% (versus 62%) of their hours below T1DM glucose levels based on porcine model [51].

Oral Insulin Delivery

The oral route is considered the best way to deliver oninsulin. It allows for the convenience of delivery via the portal circulation and it also helps with increased adherence from patients. Unfortunately, there are many obstacles to obtaining insulin this way including: degradation via proteolytic action (by pepsin, trypsin or chymotrypsin), degradation in an acidic environment (the stomach), degradation through the mucus-intestinal epithelium (the second barrier to absorption of very large molecules into your bloodstream). Large animal studies using multi-functional polymer nanoparticles with protease inhibitors (like aprotinin or soybean trypsin inhibitor) alongside permeation enhancers (like sodium caprate) and enteric coatings have collectively shown to have oral bioavailability rates of 8-15% [52,53].

Challenges and Limitations

Polymer nanoparticles designed for drug delivery present various obstacles prior to their clinical introduction, some of which are related to prior clinical/regulatory tests utilized for polymer-based DDS specifically for treatment of DM, therefore delaying their potential introduction into the clinic despite significant advancements made preclinically. Both natural and synthetic polymers, for example, are immune-active; chitosan, a natural polymer derived from chitin, elicits an acute innate immune response, as documented in humans, while synthetic polymers such as PEG result in hypersensitivity reactions following repeated dosing in 1-5% of recipients, which has resulted in anti-PEG antibody induction [54,55]. Another major obstacle to approving drugs based on natural polymers is the batch-to-batch variability of these polymers as a result of the source organism, extraction method, and degree of deacetylation and purity of the polymer after purification. In addition, in order to ensure the consistency of drug manufactured from biopolymers within a batch, it is important to process each biopolymer in the same way, manufacture using the same biopolymer processing parameters, and to adhere to the critical quality attributes (CQAs) of the biopolymer, namely

the molecular weight distribution (MWD), polydispersity (PDI), and zeta potential [56,57]. Producing polymeric nanoparticles at various commercial scales presents another significant bottleneck; therefore, microfluidic technologies including continuous microfluidic processes coupled with proven PAT methods are being examined as potential solutions to overcoming this bottleneck as they will permit scalability from bench-scale to industrial-scale GMP manufacturing while also minimizing variability (less than PDI 0.2) of commercial-sized batches of nano-carriers [58,59]. The development of appropriate regulatory frameworks to approve polymer-based nanomedicine continues to evolve and remains highly dependent upon jurisdictional considerations. For example, the FDA's guidance on drug-device combination products and the EMA's reflection papers on nanomaterials create inconsistent regulatory processes that prolong and increase the cost of developing polymer nanomedicines intended for use in DM [60].

Future Directions and Emerging Strategies

In the design of polymer drug delivery systems (DDS), artificial intelligence (AI) and machine learning (ML) are used more often to predict drug-polymer compatibility, determine release kinetics, and forecast pharmacokinetics by means of in silico methods. Experienced deep learning algorithms have trained on over 100,000 datasets of drug formulations from the literature and are able to obtain 8.3% root mean square error (RMSE) in predicting the in vitro release profiles of these formulations. The ability to predict release rates in such a short amount time will enable faster and more efficient development cycles for DDS [61,62].

The development of personalised medicine using data from pharmacogenomics, data collected by Continuous Glucose Monitoring devices and analysed by ML methodologies is a highly innovative and ever-evolving field when it comes to the design of polymer drug delivery systems. The eventual result may be the emergence of smart closed loop systems comprised of wearable biosensors, ML-based algorithms for drug release and polymer actuators that regulate drug release that can achieve better glycaemic control than current insulin pump therapy [63,64].

Extracellular vesicle (EV) mimicking polymer systems and exosome-polymer hybrid systems have been identified as the next generation of drug delivery systems, due to their superior biocompatibility, natural ability to target specific cells, and the ability to deliver the therapeutic to its intracellular target. EV/PLGA hybrid (drug loaded) nanoparticles exhibited 4.7 times greater accumulation in the pancreas of diabetic rodents than conventional PLGA nanoparticles, likely due to the presence of endogenous targeting ligands on the membrane of the vesicle [65].

A converging strategy for the development of our bio-artificial pancreas will be 3D bioprinted polymer scaffolds containing encapsulated beta cell, growth factor, and immunomodulatory agents. Alginate polymers were printed at physiological temperatures using bio-inks and contained >90% viable beta cells for 30 days after printing and had retained glucose-stimulated insulin secretion rates similar to those of fresh islets [66,67].

Table 2: Emerging Strategies and Future Directions in Polymer-Based DDS for Diabetes (2025 and beyond)

Strategy	Polymer Platform	Key Innovation	Challenge	Status (2025)
Oral Insulin Delivery	Chitosan/Alginate	Enteric-coated pH-sensitive NPs	GI enzymatic barrier	Phase II Trials
Glucose-Responsive Systems	Phenylboronic acid-PEG	Auto-adjusting insulin release	Sensitivity & specificity	Preclinical
Closed-Loop Systems	Hydrogel-PLGA hybrid	Integrated CGM-drug release	Miniaturization	Phase I Trials
Islet Encapsulation	Alginate-Barium	Immune-protected beta cells	Long-term viability	Phase II Trials
Gene Therapy Delivery	PEI-Dendrimers	Pancreatic gene correction	Off-target effects	Preclinical
Inhaled Insulin	Mannitol-PLGA	Pulmonary nano-aerosols	Variable absorption	Approved (Afrezza)
Transdermal Patches	PCL-Hydrogel	Microneedle patch arrays	Skin permeation	Phase I Trials
Exosome Mimetics	PEG-Lipid	Biomimetic drug carriers	Scale-up costs	Research Phase
AI-Personalized DDS	Smart polymers	ML-optimized formulations	Data integration	Emerging

Conclusion

This extensive review has systematically examined the relative advantages, disadvantages, and clinical development of using both natural and synthetic polymeric drug delivery systems for diabetes mellitus. Natural polymers, such as chitosan, alginate, and hyaluronic acid possess desirable biocompatibility, biodegradability, and biomimetic characteristics that allow for the effective delivery of oral insulin as well as islet encapsulation; Nonetheless, issues such as variability in the source of the polymers, potential immunogenicity, and poor mechanical properties impede their ability to be used clinically at scale. Conversely, synthetic polymers, including PLGA, PEG, PCL, and dendrimers, allow for precise manipulation of physical and chemical properties and pharmacokinetic characteristics which allow for reproducible production and compliance with regulatory standards, whilst also presenting concerns surrounding non-degradable metabolic byproducts and immunogenicity from the polymer itself. Hybrid and composite polymer designs combining the advantageous characteristics of both types of polymers have emerged with significant translational potential, particularly within glucose responsive closed-loop systems, oral insulin products, and bioartificial pancreas devices.

The incorporation of artificial intelligence-driven formulation designs, advanced bioprinting technologies, and personalized medicine paradigms represents a promising opportunity for the future of diabetes pharmacotherapeutics. It will be critical to address challenges that address immunogenicity, harmonisation of regulatory processes, and scalability of Good Manufacturing Practices in order to unlock the full potential of these advanced systems.

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