REVIEW PAPER

Advanced Polymeric Nanoparticles for Sustained Insulin Delivery in Type 1 Diabetes

[1*]Dr. Hariballav Mahapatra, [2]Dr Abhyudaya Verma, [3]Dr Sumithaa S, [4]Dr Pradip Kumar Kashyap

[1*]Consultant Diabetologist, Department of Diabetology, Sevayan Diabetes Centre, Puri, India, Email Id: nullandzero@gmail.com, Orcid Id: https://orcid.org/0000-0001-9845-0509
[2]Professor, Department of Endocrinology, Index Medical College and PG Institute Malwanchal University, Indore, MP, India, Email Id: Abhyuday9@gmail.com
[3]Tutor, MBBS, Department of Pharmacology, Sree Balaji Medical College & Hospital Bharat University, Email Id: sumithaasivakumaran19@gmail.com, Orcid Id: 0009-0003-8507-9458
[4]Assistant Professor, CGC University, Mohali, India, Email Id: pradiprgnul@gmail.com

Abstract
Type 1 diabetes necessitates life-long insulin replacement, but current delivery systems rely on insulin injections, which are not always absorbed, patients are not always able to adhere to the therapy and recreating the physiological insulin secretion is impossible. Polymeric nanoparticles have taken the place of insulin as potential prolonged carriers for insulin delivery due to their ability to protect insulin against degradation, enhance bioavailability, and control release by diffusion, polymer degradation, swelling, and glucose-responsive release. This review summarizes recent progress in polymeric nanoparticle systems for insulin delivery, with emphasis on polymer selection, formulation strategies, release mechanisms, and routes of administration, including oral, subcutaneous, transdermal, and intranasal pathways. Natural, synthetic, and hybrid polymers have all demonstrated value in improving insulin encapsulation and therapeutic performance. Advances in fabrication techniques such as double emulsion, ionic gelation, nanoprecipitation, and microfluidic preparation have further strengthened the potential of these systems. Despite encouraging progress, important translational barriers remain, including limited oral bioavailability, formulation instability, scale-up challenges, reproducibility issues, and incomplete long-term safety data. Overall, polymeric nanoparticles represent a versatile and evolving platform that may improve glycemic control and reduce treatment burden in type 1 diabetes, but successful clinical application will require standardized characterization, robust in vivo validation, and scalable, patient-acceptable designs.

Keywords: Type 1 diabetes, polymeric nanoparticles, insulin delivery, sustained release, nanocarriers
How to cite this article: Mahapatra H, Verma A, Sumithaa S, Kashyap PK. Advanced Polymeric Nanoparticles for Sustained Insulin Delivery in Type 1 Diabetes. Int J Drug Deliv Technol. 2026;16(41s): 918-927. DOI: 10.25258/ijddt.16.41s.96

1. Introduction

Type 1 diabetes mellitus (T1DM) is a persistent autoimmune disease that involves progressive destruction of pancreatic 8-cells leading to complete insulin deficiency and the inability to produce insulin independently throughout life, requiring permanent insulin replacement. The illness presents itself in a typical childish or adolescent stage, but may present itself at any age and is a major clinical and socioeconomic issue of concern across the globe[1]. Although the treatment of diabetes has improved, the problem of aspartame glycemic control persists in many people because of the intricate interaction of insulin dosage, food consumption, exercise, and individual differences in metabolism. Recent advances in disease mechanisms and treatment plans have enhanced the management of diseases; nevertheless, there are still significant possibilities of the development of novel treatment methods that would have a closer resemblance to the physiological regulation of insulin[2]. T1DM has its pathogenesis in immune-mediated 8-cell damage of the pancreas, which is caused by genetic predisposition and environmental factors. This results in compromised endogenous secretion of insulin and unregulated glucose homeostasis and eventually chronic hyperglycemia and the development of long-term complications like neuropathy, nephropathy and cardiovascular disease[3]. Since insulin replacement is necessary in order to survive, the therapeutic approaches are designed to achieve the insulin administration in the form that most closely mimics the natural pancreatic secretion without causing a high variation in the blood glucose level. To reach this, the delivery mechanisms must have the ability to produce a steady concentration of insulin in the plasma and to react effectively to the metabolic requirements.

Traditional management does use insulin therapy that is regularly based on numerous daily subcutaneous injections or continuous administration with an insulin pump. Although these methods have enhanced glycemic control, they are faced with weaknesses including discomfort on the side of the patients, lack of compliance, risk of hypoglycemia, and inability to sustain therapeutic insulin concentration[4]. Moreover, enzyme-sensitive peptide-based drugs such as insulin are cleared by the body quickly and are prone to degradation, and it is thus difficult to deliver the drugs in a controlled and extended fashion. Such constraints have provoked serious research which can be oriented towards the development of superior drug delivery platforms that would improve insulin therapeutic efficacy, bioavailability and stability. Recent progress in

*Author for Correspondence: nullandzero@gmail.com

pharmaceutical sciences has seen the creation of new drug delivery systems that are aimed at enhancing the treatment results of peptide-based drugs. The new delivery technologies aim at increasing the stability of drugs, allowing their controlled release, and improving the efficiency of targeted treatment, thus surpassing most of the challenges related to traditional formulations[5]. Among the other strategies examined, non-invasive forms of delivery like transdermal systems have been of much interest due to the possibility of decreasing the frequency of injection, and the enhanced compliance of the patient, without compromising on effective glycemic control[6]. The recent innovation in nanotechnology has proved to be a paradigm in drug delivery in the present day, with special benefits of a large surface area, physicochemical versatility, and the capacity to entrap delicate biomolecules. Nanocarrier systems are also able to shield the therapeutic agent against degradation to aid in controlled release and also increase drug absorption through biological barriers[7]. More specifically, polymeric nanoparticles have been focused on to deliver insulin because of their biodegradability, biocompatibility and ability to offer sustained drug release profiles. These nanoscale platforms are a potential platform that can enhance the insulin pharmacokinetics, as well as allow more efficient diabetes management approaches[8].

Due to the increasing demand for nanotechnology-based therapeutics, polymeric nanoparticles have become one of the top choices in delivering insulin to T1DM in a sustained manner. The purpose of this review is to discuss the current developments in the design, formulation and use of polymeric nanoparticle systems to deliver insulin. The main focus is on the principles of controlled release, formulation plans, administration routes, and existing obstacles to the transfer of these systems into clinical practice.

2. Review Methodology

This comprehensive literature review was conducted using a systematic search of the major scientific databases, such as PubMed, Scopus, Web of Science, and Google Scholar, to locate the related studies concerning polymeric nanoparticles to deliver insulin over an extended period of time in type 1 diabetes. Combined keywords were based on the keyword like insulin, polymeric nanoparticles, sustained release, formulation strategies, routes of administration, and glucose-responsive delivery. Articles were chosen according to their relevance, novelty, and value to the knowledge of nanoparticle design, release, therapeutic performance, and translational issues. Peer-reviewed articles that were in English were included, and those that were duplicated, irrelevant, or not described adequately were excluded. A critical reading of the abstracted literature was done and was categorized into thematic areas to ensure that a concise and broad overview of the current developments and future research directions is given.

3. Challenges in Conventional Insulin Delivery

Traditional insulin treatment still serves as the main way of treating diabetes, but there are still a number of issues with conventional insulin delivery strategies that still restrain the efficacy of therapy and medication compliance. Insulin preparations have been extensively developed over the last century, starting with crude animal-based preparations up to recent recombinant analogues aimed at enhancing pharmacokinetic characteristics and flexibility in route of administration. Even with these developments, the majority of the patients continue to use recurrent subcutaneous injections in order to control their glycemic levels, which may create a heavy load of treatment and influence their overall long-term adherence[9]. The convenience of patients has resulted in researchers trying to find out alternative routes of administration, especially oral administration of insulin. The theoretical benefit of oral administration is that it recreates the physiological aspects of insulin delivery via the portal circulation that may enhance metabolism regulation. But there is a high rate of insulin molecules being degraded by enzymes in the gastrointestinal tract, and the rate of insulin molecules permeating through intestinal epithelial barriers is low. Developmental solutions like ionic liquid-based carriers have thus been explored to improve insulin stability and intestinal absorption, but these methods are still in the process of development[10]. The other aspect that influences the therapeutic outcomes is the method of insulin administration. The rate and uniformity of insulin absorption may depend on parameters like injection depth, needle length, site selection and so forth. It has been clinically proven that the incorrect injection methods can result in uneven delivery of drugs and add to the variability of blood glucose levels, which underlines the necessity of relying on all traditional insulin treatment methods on the implementation of appropriate injection practices[11].

The developments of technology have led to insulin delivery machines that are automated, meant to enhance the regulation of glucose levels. The closed-loop insulin delivery technologies combine a continuous glucose monitor and a programmable insulin pump to vary the insulin delivery based on current glucose readings. These systems have been shown to have better glycemic control in controlled clinical settings; however, their complexity, high cost, and dependency on advanced equipment might hamper a wide-scale clinical use[12]. Glycemic variability is a significant clinical issue in standard insulin treatment. The changes in blood glucose levels occur because of differences in the absorption of insulin, metabolic reactions, lifestyle, and individual patient physiological conditions. The repeated glycemic fluctuations are linked to higher risks of acute and chronic complications, hence the necessity of delivering modes that can ensure a more stable amount of insulin in the body[13]. Besides pharmacokinetic restrictions, one more significant issue is insulin stability in storage and handling. Being a protein-based therapeutic agent, insulin is vulnerable to environmental factors like changes in temperature and poor storage habits. Living under adverse conditions could threaten structural integrity and biological activity, thereby lowering the therapeutic efficacy and possibly patient safety[14].

The traditional formulations of insulin also have a challenge in the delivery of sustained and predictable

insulin release. A significant number of the existing formulations are aimed at causing rapid or intermediate pharmacological effects, which may need multiple daily administrations in order to provide sufficient glycemic control. To enhance therapeutic consistency, controlled drug delivery systems have been considered to prolong drug action and thus ensure long-term regulated insulin release, although the regulated insulin release is difficult to achieve with the traditional formulations[15]. All these shortcomings, such as injection burden, glycemic variability, storage instability and poor bioavailability by other routes of administration, underpin the importance of new technologies in insulin delivery. The recent studies have paid growing attention to the more advanced carrier systems, such as nanocarrier-based systems, that seek to provide better insulin stability, increase bioavailability, and allow the sustained therapeutic release. These strategies have shown good potential to address the limitations of the traditional insulin treatment method and enhance better long-term diabetes management outcomes[16]. Figure 1 summarizes the main disadvantages of the traditional insulin treatment.

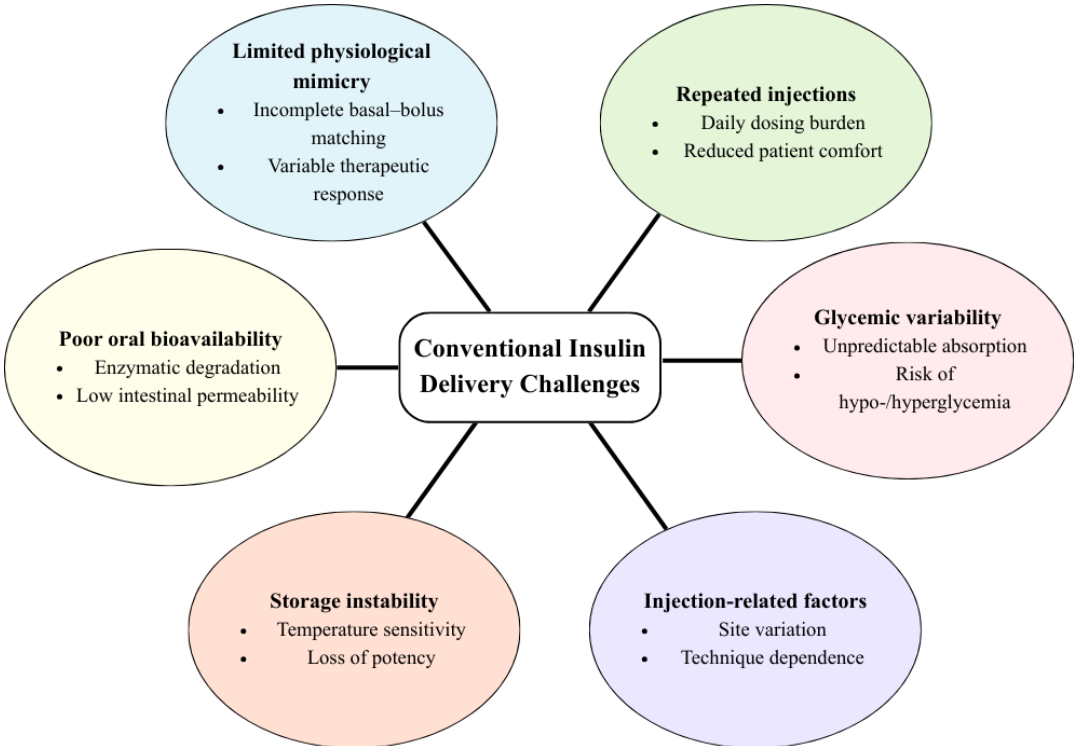

Figure 1. Major challenges in conventional insulin delivery

4. Polymeric Nanoparticles as Drug Delivery Systems

4.1 Overview of Polymeric Nanoparticles

Polymeric nanoparticles have become one of the most reliable tools in the contemporary drug delivery field because they can optimize the therapeutic effect, stabilize drugs and also allow the control of the drug release. These nanoscale vectors are largely based on biodegradable and biocompatible polymers that are capable of loading active pharmaceutical agents into a polymer or core-shell format. Their small size and adjustable surface properties help them to interact better with living systems whilst protecting the drugs against early degradation. Consequently, polymeric nanoparticles have been extensively studied as efficient agents to deliver different therapeutic molecules such as small molecules, proteins, and nucleic acids[17]. The recent advancements in nanotechnology have greatly increased the potential of the polymeric nanoparticles in pharmaceutical applications. The development of polymer chemistry and methods of nanoparticles fabrication has allowed to accurately control of the properties of nanoparticles (size, morphology, and surface activity). These properties make it possible to design systems of delivery that have the ability to enhance drug loading effectiveness, improve stability and attain controlled drug release patterns. As a consequence, polymeric nanoparticles are also becoming considered as potential carriers of targeted and sustained drug delivery in numerous therapeutic fields[18].

4.2 Delivery of Protein and Peptide Therapeutics

This makes the delivery of protein and peptide drugs quite challenging because they are structurally complicated, large molecules, and prone to enzymatic breakdown. The traditional drug delivery systems do not preserve the stability and bioavailability of these biomolecules, leading to decreased therapeutic efficacy. Hence, protein and peptide drugs escaped through administration and transportation in the body, need specialized carrier systems to maintain their safety[19]. Therapeutics on the basis of peptides are supposed to have delivery systems that can maintain their biological functions and, at the same time, allow easy absorption and distribution. Their high hydrophilia and weak molecular fold enable them to be especially susceptible to denaturation and quick clearance. Nanocarrier-based systems, particularly polymeric nanoparticles, provide a shielding effect which can be used to increase stability

and provide a sustained release effect, thus enhancing the treatment efficacy of peptide drugs[20]. Inclusion of insulin inside biodegradable polymeric scaffolds has been a common subject of research in a bid to enhance its pharmacokinetic characteristics. Polymeric carriers have the potential of protecting insulin against degradation and release insulin gradually by polymer diffusion and degradation processes. This type of system can provide a sustained level of therapeutic insulin and a decreased lapse between drug delivery, which is especially useful in chronic illnesses like diabetes[21].

4.3 Physicochemical Properties and Release Mechanisms

Physicochemical properties of polymeric nanoparticles are the major factors determining their performance as a drug delivery system. The size of particles, surface charge, morphology, and polymer composition are important factors that influence the stability of nanoparticles, the route of biodistribution, cellular uptake, and interaction with biological conditions. These features thus need to be carefully optimized in order to achieve efficient drug delivery and reduce any possible adverse biological reaction[22]. The other notable benefit of polymeric nanoparticle systems is that it is possible to control drug release using various kinetic reactions. Polymer degradation, polymer swelling, diffusion or a combination of all three can be used to release drugs out of a polymer matrix. Knowledge and management of such release kinetics are also very important to design delivery systems that are able to sustain therapeutic drug levels over long periods of time, especially in curing chronic illnesses that need continuous treatment[23]. The simplified functional scheme of polymeric nanoparticles is shown in Figure 2, as well as the main characteristics that define their behaviour in insulin delivery.

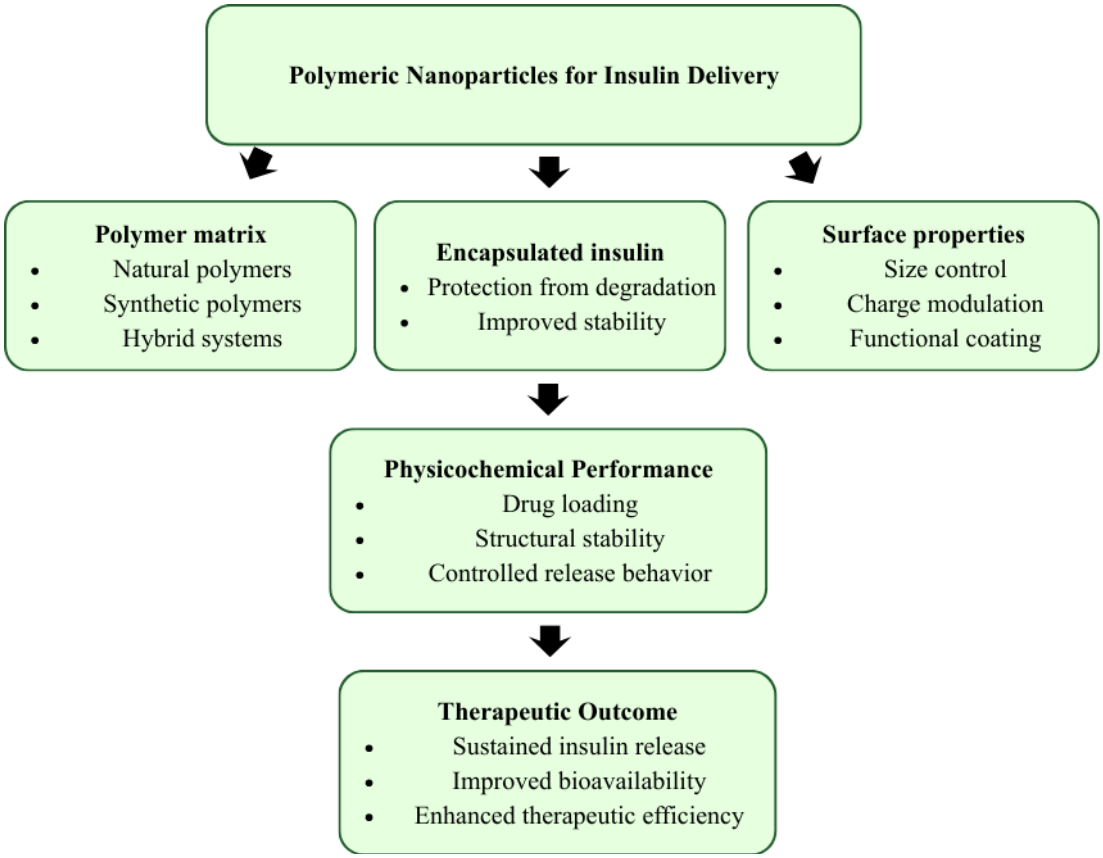

Figure 2. Functional design of polymeric nanoparticles for insulin delivery

5. Types of Polymers Used in Insulin Nanoparticle Formulations

The design of the polymeric nanoparticles to deliver insulin is dependent on the appropriate choice of polymeric materials, which can then protect insulin, enhance the stability of the insulin and provide the ability to release the drug in a controlled manner. The polymers in nanoparticle formulations should have the following properties: biocompatibility, biodegradability, and the capability to entrap delicate biomolecules without affecting their biological activities. Natural and synthetic polymers have been widely researched for use as insulin nanoparticle systems because of their desirable physicochemical and pharmacological properties[24].

5.1 Natural Polymers

The use of natural polymers is the most explored in insulin nanoparticle formulations due to the biocompatibility of polymers and low toxicity. Natural polymers tend to be highly biologically compatible and can also be effectively allowed to interact with the membranes of biology, potentially increasing drug absorption and therapeutic efficacy. Natural polymers

are an efficient encapsulation system of peptide drugs in the case of insulin delivery and guarding them against enzymatic degradation[25]. Chitosan is one of the natural polymers that has been widely investigated owing to its mucoadhesive and permeation-promoting characteristics. Chitosan nanoparticles should be used because they will allow the particles to interact with biological tissues better and improve the conduction of drugs across biological barriers. Engineered chitosan nanoparticles have shown encouraging results in attentive insulin delivery in experimental systems in formulation studies, and thus, they can be applied in advanced insulin delivery functions[26].

5.2 Synthetic Polymers

Nanoparticle systems are common in synthetic polymers due to the increased ability of synthetic polymers to control physicochemical properties like molecular weight, degradation rate, and structural stability. The most commonly used materials in the insulin nanoparticle formulations are poly(lactic-co-glycolic acid), polyethene glycol and polycaprolactone. The polymers enable the accurate control of nanoparticle size, drug loading capacity and release kinetics, and their use is appropriate in the design of sustained-release insulin delivery systems[27]. The use of synthetic polymers in drug delivery systems also allows the making of nanoparticles of high structural integrity and with reproducible manufacturing properties. These materials may be designed to maximize the insulin encapsulation and control its release by the use of polymer degradation or diffusion, and increase therapeutic efficacy in diabetes management[28].

5.3 Modified and Hybrid Polymer Systems

Current studies have been directed at the creation of modified polymeric systems in a bid to enhance the performance of insulin nanoparticles. Adjusted polymeric nano-formulations are capable of controlling the binding and the release of insulin by modifying the interaction of polymers and their structural alterations. These systems enable better control over drug release behaviour and can be useful in improving pharmacokinetic behaviour in pharmacokinetic insulin delivery[29]. Besides polymer modification, the method of fabrication applied when preparing nanoparticles also affects the functionality of the insulin delivery system. The emulsion-based approaches, nanoprecipitation, and solvent evaporation have been investigated as methods of producing insulin-loaded polymeric nanoparticles with maximized size, encapsulation efficiency, and release characteristics[30]. Moreover, nanoparticles of polymer, which undergo biodegradation, have been extensively explored in oral insulin delivery. The systems are meant to prevent the gastrointestinal breakdown of insulin and increase the intestinal absorption using appropriate polymer matrices. It has been shown that nanoparticle formulations developed using various biodegradable polymers can enhance the stability of insulin and its bioavailability, and this technology can be used as a novel advanced drug delivery system in the treatment of diabetes[31]. The key polymer groups employed in the preparation of insulin nanoparticles, functional benefits, drawbacks, and applicability in sustained insulin administration are summarized in Table 1. Figure 3 displays a simplified scheme of polymer choice in the design of the insulin nanoparticle.

Table 1. Major polymer classes used in insulin nanoparticle formulations

Polymer class	Representative examples	Key functional advantage	Main limitation	Typical relevance to insulin delivery
Natural polymers	Chitosan, alginate, dextran, gelatin	High biocompatibility and mild encapsulation conditions	Batch variability and lower mechanical strength	Useful for mucoadhesive and absorption-enhancing systems
Synthetic polymers	PLGA, PCL, PEG-based polymers	Better control over degradation and release behavior	Possible burst release or formulation complexity	Suitable for sustained and reproducible insulin release
Hybrid polymers	Natural–synthetic combinations	Combines bioactivity with structural stability	More complex formulation optimization	Improves balance between loading, protection, and release
Modified polymers	Thiolated or functionalized derivatives	Enhanced binding, targeting, or responsiveness	Additional synthesis and characterization required	Supports tailored release and improved insulin stability

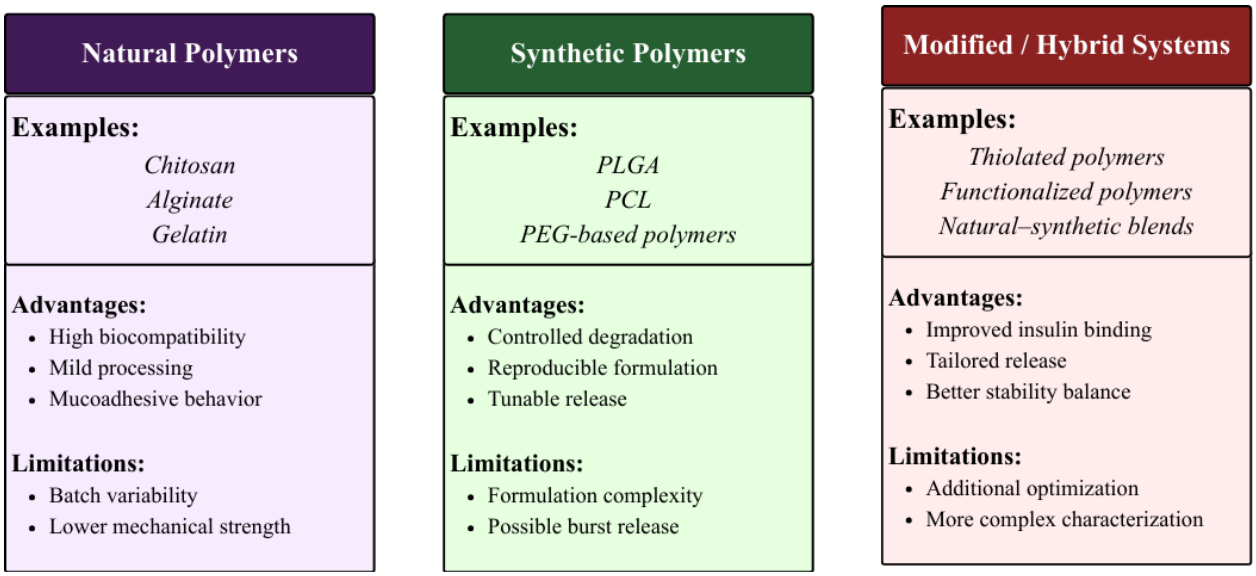

Figure 3. Polymer selection strategy for insulin nanoparticle formulation

6. Formulation Strategies for Polymeric Insulin Nanoparticles

The polymeric nanoparticle insulin delivery needs serious consideration of the methods of preparation that do not alter the structure of insulin, but, on the contrary, provide the efficient encapsulation of the insulin and the controlled release. Since insulin is a sensitive peptide that is easy to degrade and denature, formulation measures should utilize mild processing conditions and appropriate polymer systems to retain the biological activity of insulin. Different methods of nanoparticle fabrication have thus been implemented to enhance the loading efficiency of drugs, stability of the particle and kinetics of release in an insulin delivery system[32].

6.1 Double Emulsion Solvent Evaporation

A technique that is most popular in the production of insulin-loaded polymeric nanoparticles, especially with hydrophilic drugs, is the double emulsion solvent evaporation method. This is done by means of an aqueous insulin solution being emulsified in an organic phase with a biodegradable polymer to create a primary water-in-oil emulsion. This initial emulsion is again re-emulsified in an external aqueous solution to form a water-oil-water system, and solvent evaporation is then conducted to form nanoparticles. The approach facilitates the effective encapsulation of insulin and permits the control of the particle properties through altering the parameters of the formulations, including the polymer concentration and the type of stabilizer[33].

6.2 Microfluidic-Assisted Nanoparticle Preparation

Recently, techniques of fabrication with microfluidics have attracted attention to the manufacture of nanoparticles using polymers with high uniformity and reproducibility. These systems employ the use of controlled micro-scale channels in the regulation of fluid mixing and nanoparticle formation under highly precise conditions. Microfluidic methods offer superior control of particle size distribution, encapsulation efficiency and stability compared to the traditional emulsion-based methods. This kind of control over formulation parameters renders microfluidic-aided preparation an excellent approach towards advanced insulin nanoparticle systems development[34].

6.3 Ionic Gelation Technique

Nanoparticles made out of natural polymers like chitosan are normally prepared using the ionic gelation method. The method is based on the electrostatic interactions between oppositely charged molecules in the form of nanoparticles and crosslinking agents to create stable structures in nanoparticles under mild conditions. Ionic gelation has some benefits, especially in the encapsulation of sensitive biomolecules such as insulin, since harsh organic solvents and high processing temperatures are eliminated. Enhanced ionic gelation systems have proven to have better encapsulation efficiency and regulated drug release properties in the insulin nanoparticle systems[35].

6.4 Nanoprecipitation Method

Another common technique that has been used in the production of polymeric nanoparticles and, in particular, peptide and protein therapeutics is nanoprecipitation. In this method, the polymer solution of the drug is quickly added to a non-solvent phase, causing spontaneous nanoparticle formation in the form of polymer precipitation. Nanoprecipitation techniques that do not involve water have also been established to reduce peptide denaturation and enhance the drug loading efficiency. Such systems are able to produce nanoparticles with a non-dispersed size and greater stability; thus, they are applicable when using them in peptide drug delivery[36].

6.5 Gel-Based Delivery Systems

Another new approach to insulin delivery is a gel-based system, especially in the preparation of sustained and responsive drug delivery systems. Insulin-loaded nanoparticles can be placed inside the polymeric gels

and hydrogels to have a longer period of drug release and better therapeutic control. They have discussed the use of these systems as both constant and glucose-reactive insulin delivery that could offer the potential to maintain the stability of insulin and lower the number of insulin doses in the management of diabetes[37]. Table 2 provides a comparative data of the key formulation methods that have been employed to prepare polymeric insulin nanoparticles.

Table 2. Common formulation strategies for polymeric insulin nanoparticles

Formulation strategy	Basic principle	Major advantage	Key limitation	Common outcome
Double emulsion solvent evaporation	Entrapment of insulin in water–oil–water emulsion followed by solvent removal	Widely used for hydrophilic drugs	Risk of insulin leakage and batch variability	Good encapsulation with tunable particle characteristics
Microfluidic-assisted preparation	Controlled mixing in microchannels for nanoparticle formation	Excellent size uniformity and reproducibility	Requires specialized equipment	Improved control over particle size and stability
Ionic gelation	Electrostatic interaction between polymer and crosslinker	Mild conditions suitable for peptides	Limited polymer compatibility	Efficient encapsulation with reduced processing stress
Nanoprecipitation	Polymer precipitation after solvent displacement	Simple and rapid preparation	May affect loading efficiency for hydrophilic drugs	Narrow particle size distribution
Gel-based incorporation	Embedding nanoparticles or insulin in gel matrices	Prolonged and sometimes responsive release	Formulation complexity	Sustained insulin release with reduced dosing frequency

7. Mechanisms of Sustained Insulin Release

Insulin delivery systems are sustained systems which are aimed at sustaining therapeutic concentrations of forms of drugs over long durations, whilst showing minimal variation in the level of blood glucose. Controlled insulin release is especially significant in the management of diabetes since the process enables them to replicate physiological insulin secretion and avoids the high administration frequency. Polymer nanoparticle systems offer a number of ways in which insulin may be released in slow amounts; they include diffusion, polymer breakdown, swelling release, and glucose-sensitive mechanisms. The mechanisms involve the need to comprehend them so that the development and implementation of delivery systems that are capable of long-term glycemic control and enhanced therapeutic outcomes can be achieved[38].

7.1 Diffusion-Controlled Release

One of the most prevalent mechanisms that controls the release of drugs out of polymeric nanoparticles is diffusion-controlled release. The insulin molecules are released into the biological environment through the polymer matrix or nanoparticle surface in this process, and the molecules diffuse through the polymer matrix or nanoparticle surface. Diffusion rate is also determined by a variety of factors that include polymer composition, particle size, drug loading, and the physicochemical properties of the encapsulated drug. These parameters can be adjusted to allow diffusion-based systems to deliver gradual and predictable insulin release over prolonged durations, which can be useful to achieve constant levels of blood glucose[39].

7.2 Degradation-Controlled Release

Another mechanism that has facilitated sustained release of insulin by nanoparticle systems is polymer degradation. Gradually, the polymer chains of biodegradable polymer matrices release the insulin molecules that are encapsulated. In this process, the release duration of the drug can be prolonged and the period of therapy enhanced. It has been established that insulin complexes that have been loaded into polymeric carriers can sustain long-term glycemic control because of the continuous release of the complex due to progressive degradation of the polymer network within the biological environment[40].

7.3 Swelling and Hydrogel-Based Release

There are certain polymeric systems that make use of swelling to control insulin release. When placed in these systems, the polymer networks absorb water in the environment surrounding them and swell to form channels through which insulin molecules can diffuse. The hydrated hydrogel-based system is most adaptable to such mechanisms as the hydrated structure allows the controlled swelling and release of the drug. Protein-polymer hydrogel has been considered in insulin delivery and is promising in in situ formation and sustained release profile with physiological conditions[41].

7.4 Glucose-Responsive Release Systems

Glucose-sensitive delivery systems are the new-generation approach of insulin release that is developed to resemble the physiological reaction of pancreatic 8-cells. The systems are designed to secrete insulin due to

the increased glucose level, which delivers self-regulated drug delivery. Different materials and carrier systems have been created which react to glucose concentration by either an enzyme reaction, a glucose binding molecule or an alteration in the polymer structure. These intelligent delivery systems have a lot of potential in the treatment of diabetes since they can perform insulin release that can be switched to meet changes in metabolism[42]. The recent studies have also gone a step further to design glucose-responsive insulin delivery platforms that can be used to translate the laboratory innovations into clinical practice. These systems combine responsive polymers and nanomaterials, which respond in a dynamic manner to the level of blood glucose and release insulin. It is possible to achieve better glycemic control and minimize the chances of hypoglycemia by uniting controlled release processes and glucose responsiveness, which is one of the promising paths of next-generation insulin delivery regimes[43].

8. Routes of Administration for Polymeric Insulin Nanoparticles

Polymeric insulin nanoparticles' therapeutic performance also largely depends on the route of administration, as the various pathways entail different physiological barriers, absorption properties and formulation needs. The choice of a proper route is thus necessary to decrease the insulin deterioration, enhance bioavailability, and attain prolonged glycemic regulation. The recent development in nanoparticle design has greatly increased the utility of various modes of delivery other than traditional modes of administration of drugs, especially in enhancing patient compliance and decreasing the expenses of having to administer drugs repeatedly[44].

8.1 Oral Administration

Oral delivery is one of the most preferred ways of administration of insulin due to its convenience, patient acceptability, and its ability to replicate the physiological pathway of endogenous insulin by use of portal circulation. But the oral insulin has some significant obstacles, such as acidic gastric environments, enzyme breakdown, and poor intestinal permeability. To address these limitations, polymeric nanoparticles have been studied to the point of guarding insulin in biodegradable scaffolds and mucosal uptake through improved oral bioavailability and decreasing treatment efficacy[44].

8.2 Subcutaneous Administration

Subcutaneous delivery has remained the most common route in which insulin is delivered, and it is very relevant in polymeric nanoparticle formulations. Subcutaneous systems based on nanoparticles can be used as depot vehicles which release insulin at slow rates over long periods, thus decreasing the frequency of injections and enhancing pharmacokinetic predictability. Recent developments in subcutaneous biomacromolecule delivery have been concentrated on higher tolerance with tissue, reduced burst release and improved sustained release dynamics of the nanoparticle systems in the treatment of diabetes[45].

8.3 Transdermal Administration

Transdermal delivery is a non-invasive method of delivering drugs as opposed to injections and has received significant interest with regard to insulin delivery. Due to the significant interference caused by the stratum corneum towards peptide delivery, polymeric nanoparticle systems are frequently combined with advanced penetration methods to enhance transdermal delivery. One of the most promising solutions has been the micro and nanoneedle-assisted systems, which have the ability to form transient microchannels in the skin and allow efficient delivery of insulin with little painful experiences, increasing delivery efficacy and tolerability[46]. Besides the use of microneedle strategies, polymeric transdermal systems, including films, gels, patches, and nanoparticle-loaded matrices, have also been investigated in sustained insulin delivery. These systems have the benefit of controlled drug delivery, enhanced skin compliance and decreased invasiveness. Their implication of giving sustained therapeutic effect and the absence of degradation in the gastrointestinal tract make them desirable in the future insulin delivery scaffolds[47].

8.4 Intranasal Administration

Non-invasive routes of administration of insulin have attracted attention to the intranasal route as a highly vascularized mucosal surface with high potential systemic absorption. Nasal delivery has the potential to circumvent first-pass metabolism and therefore provide more therapeutic options, especially where targeting the central nervous system is required. The recent findings have put a lot of emphasis on the possibilities of nasal insulin administration as a way of controlling glycemic cases and as a way of addressing neurological implications, as the range of administration routes continues to expand[48]. The latest developments in nasal insulin administration focus on the application of special carriers and mucoadhesive agents to enhance the retention period, insulin resistance to enzyme breakdown, as well as epithelial carriage. Nanoparticle polymeric formulations are specifically appropriate in this route, as they may enhance mucosal contact, and they may assist in the maintenance of the release behavior. Despite the need for additional optimization, intranasal delivery is also a promising option to use in future insulin nanomedicine applications[49]. Table 3 is a comparison of the key administration routes studied in relation to polymeric insulin nanoparticles, the benefits of this approach, biological impediments and the potential application in translation.

Table 3. Routes of administration for polymeric insulin nanoparticles and their advantages and barriers

Route	Main advantage	Major biological barrier	Delivery goal	Current translational status
Oral	High patient acceptability and physiological portal pathway	Enzymatic degradation and poor intestinal permeability	Improve bioavailability and reduce injection burden	Promising but still limited by inconsistent absorption
Subcutaneous	Established clinical route with predictable administration	Injection burden and local variability in absorption	Prolonged depot-like release	Most clinically practical for near-term application
Transdermal	Non-invasive and potentially painless delivery	Stratum corneum barrier	Improve adherence through sustained skin-based delivery	Advancing with microneedle and polymer-assisted systems
Intranasal	Rapid absorption and avoidance of first-pass metabolism	Limited residence time and mucosal clearance	Enhance non-invasive systemic or targeted delivery	Promising but requires further optimization

9. Current Research Advances, Challenges and Future Research

The recent advances in the delivery of insulin have shifted the traditional form of insulin injections to systems that are more user-friendly and more in-touch with technology. Of these, insulin delivery via microneedles has been seen as a viable minimally invasive intervention that can enhance compliance levels in patients as well as improve transdermal insulin delivery. These systems are associated with painless administration as well as the potential of controlled release, but the dilemmas associated with dose loading, mechanical strength, mass production and stability over time continue to restrain their further clinical translation[50]. Similar to the innovations that rely on materials, the technologies of automated insulin delivery have improved over recent years significantly. Practical research on open-source automated insulin delivery systems has also shown promising results in the areas of safety, glycemic regulation, and patient satisfaction, indicating the increased role of digital and patient-centred approaches in diabetes management[51]. Automated insulin delivery has also spilt into the wider diabetes care discourse, with the development of more interest in changing these systems to suit more patient groups and enhance algorithm-driven insulin control[52].

Oral administration of insulin has also been a key area of current research due to its potential of enhancing convenience and its ability to depict physiological delivery of insulin via the portal circulation. Recent nanosystems have also used a wide variety of materials and architectures, which help to protect insulin against gastrointestinal degradation, enhance epithelial-to-epithelial transport, and increase systemic absorption. These oral nanoplatforms are versatile and represent a dramatic change in the multifunctional design of carriers and indicate the maturity of insulin formulations that involve nanotechnology[53]. In spite of these advances, there are still significant obstacles such as enzyme degradation, low permeability, gastrointestinal instability and uneven bioavailability, all of which are still limiting successful clinical translation[54]. Besides the formulation and device-related developments, the larger issue of the establishment of new insulin delivery systems into the standard practice context is not that trivial. The possibilities of next-generation diabetes technologies, as well as their complexity, can be described with the help of open-source and automated delivery platforms. Problems concerning regulatory control, interoperability of these devices, user education, cost, and reliability of the data should be addressed prior to the adoption of such systems in the common clinical practice[55].

In prospective studies, it is desirable that future research should focus on designing insulin delivery systems that are able to combine sustained release, glucose responsiveness, biocompatibility and ease of administration at scalable and cost-effective systems. There is also a requirement to put more emphasis on the long-term safety studies, reproducible manufacturing techniques and translational evaluation in populations that are relevant in practice. The intersection of biomaterials science, nanotechnology and digital therapeutics will probably constitute the next stage of innovation, and the end result is more effective, yet more accessible and patient-centered insulin delivery systems.

10. Conclusion

Polymeric nanoparticles are one approach that is otherwise a highly promising insulin delivery method in type 1 diabetes since they are capable of shielding insulin against degradation, enhancing bioavailability and regulating insulin delivery by diffusion, degradation, swelling, and glucose-responsive processes. They are versatile and can be formulated using natural, synthetic, and hybrid polymers and adapted to be given by oral, subcutaneous, transdermal, and intranasal routes. The current advances in formulation technologies and intelligent delivery design have further enhanced their ability to minimize injection load, minimize glycemic fluctuations, and provide more physiological insulin replacement. Although these improvements have been made, significant obstacles persist, such as instability of formulation, low oral bioavailability, scale-up challenges, reproducibility, long-term safety and translational uncertainty. The

clinical adoption will also be based on the development of systems that integrate sustained release and glucose responsiveness, biocompatibility, manufacturability and acceptability by the patients at a reasonable cost. In general, the field of polymeric insulin nanoparticles is shifting away from proof-of-concept into translational relevance, which will have to be reinforced with stronger in vivo demonstration, standard characterization, and design with clinical implications.

References

1. Syed FZ. Type 1 diabetes mellitus. Annals of internal medicine. 2022 Mar;175(3):ITC33-48.
2. Powers AC. Type 1 diabetes mellitus: much progress, many opportunities. The Journal of clinical investigation. 2021 Apr 15;131(8).
3. Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. Endocrine connections. 2018 Jan 1;7(1):R38-46.
4. Olorunsola EO, Alozie MF, Davies KG, Adedokun MO. Advances in the science and technology of insulin delivery: A review. Journal of Applied Pharmaceutical Science. 2021 Jul 18;11(8):184-91.
5. Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike UG. Advances in drug delivery systems, challenges and future directions. Heliyon. 2023 Jun 1;9(6).
6. Zhang Y, Yu J, Kahkoska AR, Wang J, Buse JB, Gu Z. Advances in transdermal insulin delivery. Advanced drug delivery reviews. 2019 Jan 15;139:51-70.
7. Prabhakar P, Banerjee M. Nanotechnology in drug delivery system: Challenges and opportunities. Journal of Pharmaceutical Sciences and Research. 2020 Apr 1;12(4):492-8.
8. Sahu T, Ratre YK, Chauhan S, Bhaskar LV, Nair MP, Verma HK. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. Journal of Drug Delivery Science and Technology. 2021 Jun 1;63:102487.
9. Bolli GB, Cheng AY, Owens DR. Insulin: evolution of insulin formulations and their application in clinical practice over 100 years. Acta Diabetologica. 2022 Sep;59(9):1129-44.
10. Banerjee A, Ibsen K, Brown T, Chen R, Agatemor C, Mitragotri S. Ionic liquids for oral insulin delivery. Proceedings of the National Academy of Sciences. 2018 Jul 10;115(28):7296-301.
11. Yuan L, Li F, Jing T, Ding B, Luo Y, Sun R, Wang X, Diao H, Su X, Ye L, Ma J. Insulin injection technique is associated with glycemic variability in patients with type 2 diabetes. Diabetes Therapy. 2018 Dec;9(6):2347-56.
12. Bally L, Thabit H, Hartnell S, Andereggen E, Ruan Y, Wilinska ME, Evans ML, Wertli MM, Coll AP, Stettler C, Hovorka R. Closed-loop insulin delivery for glycemic control in noncritical care. New England Journal of Medicine. 2018 Aug 9;379(6):547-56.
13. Nwadiugwu MC, Bastola DR, Haas C, Russell D. Identifying glycemic variability in diabetes patient cohorts and evaluating disease outcomes. Journal of clinical medicine. 2021 Apr 2;10(7):1477.
14. Heinemann L, Braune K, Carter A, Zayani A, Krämer LA. Insulin storage: a critical reappraisal. Journal of diabetes science and technology. 2021 Jan;15(1):147-59.
15. Tran TT, Tran PH. Controlled release film forming systems in drug delivery: the potential for efficient drug delivery. Pharmaceutics. 2019 Jun 20;11(6):290.
16. Sriram N, Parasakthi N. Overcoming challenges in oral insulin delivery: innovations in nanocarrier systems for enhanced bioavailability. Scientific Hub of Applied Research in Emerging Medical science & technology. 2024 Aug 14;3(4):1-7.
17. Begines B, Ortiz T, Pérez-Aranda M, Martínez G, Merinero M, Argüelles-Arias F, Alcudia A. Polymeric nanoparticles for drug delivery: Recent developments and future prospects. Nanomaterials. 2020 Jul 19;10(7):1403.
18. Beach MA, Nayanathara U, Gao Y, Zhang C, Xiong Y, Wang Y, Such GK. Polymeric nanoparticles for drug delivery. Chemical reviews. 2024 Apr 16;124(9):5505-616.
19. Yadav AR, Mohite SK. Recent advances in protein and peptide drug delivery. Research journal of pharmaceutical dosage forms and technology. 2020;12(3):205-12.
20. Charan N. Protein and peptide drug delivery. Smart Drug Deliv. 2022 Jul 6;12:39.
21. Yerlan GY, Tyussyupova BB, Tazhibayeva SM, Musabekov KB, Balabushevich NG, Kokanbayev AK. Encapsulation of Insulin in Biodegradable Polymers. Eurasian Chemico-Technological Journal. 2022 Dec 28;24(4):351-61.
22. Yusuf A, Almotairy AR, Henidi H, Alshehri OY, Aldughaim MS. Nanoparticles as drug delivery systems: a review of the implication of nanoparticles' physicochemical properties on responses in biological systems. Polymers. 2023 Mar 23;15(7):1596.
23. Paarakh MP, Jose PA, Setty CM, Peterchristoper GV. Release kinetics–concepts and applications. International Journal of Pharmacy Research & Technology (IJPRT). 2018;8(1):12-20.
24. Hadiya S, Radwan R, Zakaria M, El-Sherif T, Hamad MA, Elsabahy M. Nanoparticles integrating natural and synthetic polymers for in vivo insulin delivery. Pharmaceutical development and technology. 2021 Jan 2;26(1):30-40.
25. Mansoor S, Kondiah PP, Choonara YE, Pillay V. Polymer-based nanoparticle strategies for insulin delivery. Polymers. 2019 Aug 22;11(9):1380.
26. Rathore P, Mahor A, Jain S, Haque A, Kesharwani P. Formulation development, in vitro and in vivo evaluation of chitosan engineered nanoparticles for

ocular delivery of insulin. RSC advances. 2020;10(71):43629-39.
27. Satchanska G, Davidova S, Petrov PD. Natural and synthetic polymers for biomedical and environmental applications. Polymers. 2024 Apr 20;16(8):1159.
28. Al-Hashimi N, Babenko M, Saaed M, Kargar N, ElShaer A. The impact of natural and synthetic polymers in formulating micro and nanoparticles for anti-diabetic drugs. Current Drug Delivery. 2021 Feb 1;18(3):271-88.
29. Namazi N. A Modified Polymeric Nano-formulation to Control Binding and Release of Insulin. Journal of Pharmaceutical Sciences. 2022 Sep 1;111(9):2481-9.
30. Wong CY, Al-Salami H, Dass CR. Fabrication techniques for the preparation of orally administered insulin nanoparticles. Journal of Drug Targeting. 2021 Apr 21;29(4):365-86.
31. Kassem M, Ali A, El-Assal M, El-Badrawy A. Formulation, characterization and in vivo application of oral insulin nanotechnology using different biodegradable polymers: advanced drug delivery system. Int J Pharm Sci Res. 2018 Sep 1;9(9):3664-77.
32. Wang Y, Li H, Rasool A, Wang H, Manzoor R, Zhang G. Polymeric nanoparticles (PNPs) for oral delivery of insulin. Journal of nanobiotechnology. 2024 Jan 3;22(1):1.
33. Haggag YA, Faheem AM, Tambuwala MM, Osman MA, El-Gizawy SA, O'Hagan B, Irwin N, McCarron PA. Effect of poly (ethylene glycol) content and formulation parameters on particulate properties and intraperitoneal delivery of insulin from PLGA nanoparticles prepared using the double-emulsion evaporation procedure. Pharmaceutical development and technology. 2018 Apr 21;23(4):370-81.
34. Kouhjani M, Jaafari MR, Kamali H, Abbasi A, Tafaghodi M, Mousavi Shaegh SA. Microfluidic-assisted preparation of PLGA nanoparticles loaded with insulin: a comparison with double emulsion solvent evaporation method. Journal of Biomaterials science, Polymer edition. 2024 Feb 11;35(3):306-29.
35. Mahdizadeh Barzoki Z, Emam-Djomeh Z, Rafiee-Tehrani M, Mortazavian E, Moosavi Movahedi AA. Optimization and development of insulin nanoparticles by new thiolated chitosan derivative with ionic gelation method using a model-based methodology. Journal of Food and Bioprocess Engineering. 2019 Jun 1;2(1):25-34.
36. Zada MH, Rottenberg Y, Domb AJ. Peptide loaded polymeric nanoparticles by non-aqueous nanoprecipitation. Journal of Colloid and Interface Science. 2022 Sep 15;622:904-13.
37. Taylor MJ, Chauhan KP, Sahota TS. Gels for constant and smart delivery of insulin. British Journal of Diabetes. 2020 Jun 5;20(1):41-51.
38. Zhang Y, Austin MJ, Chou DH. Insulin stabilization designs for enhanced therapeutic efficacy and accessibility. Accounts of Chemical Research. 2024 Oct 28;57(22):3303-15.
39. Wang S, Liu R, Fu Y, Kao WJ. Release mechanisms and applications of drug delivery systems for extended-release. Expert Opinion on Drug Delivery. 2020 Sep 1;17(9):1289-304.
40. Sharma D, Singh J. Long-term glycemic control and prevention of diabetes complications in vivo using oleic acid-grafted-chitosan-zinc-insulin complexes incorporated in thermosensitive copolymer. Journal of Controlled Release. 2020 Jul 10;323:161-78.
41. Ali A, Saroj S, Saha S, Rakshit T, Pal S. In situ-forming protein-polymer hydrogel for glucose-responsive insulin release. ACS Applied Bio Materials. 2023 Jan 10;6(2):745-53.
42. Yao Y, Ji K, Wang Y, Gu Z, Wang J. Materials and carriers development for glucose-responsive insulin. Accounts of Materials Research. 2022 Jul 29;3(9):960-70.
43. Wang J, Wang Z, Yu J, Kahkoska AR, Buse JB, Gu Z. Glucose-responsive insulin and delivery systems: innovation and translation. Advanced Materials. 2020 Apr;32(13):1902004.
44. Limenh LW. A review on oral novel delivery systems of insulin through the novel delivery system formulations: A review. SAGE open medicine. 2024 Jan;12:20503121231225319.
45. Li C, Wan L, Luo J, Jiang M, Wang K. Advances in subcutaneous delivery systems of biomacromolecular agents for diabetes treatment. International Journal of Nanomedicine. 2021 Feb 17:1261-80.
46. Jan Z, Mohammadi M, Mollazadeh S, Abnous K, Taghdisi SM, Danesh A, Ramezani M, Alibolandi M. Micro and nanoneedles for transdermal delivery of insulin. Journal of Drug Delivery Science and Technology. 2025 Sep 1;111:107128.
47. Darvishha S, Amiri S. (Trans) dermal insulin delivery based on polymeric systems. International Journal of Polymeric Materials and Polymeric Biomaterials. 2019 Dec 12;68(18):1118-32.
48. Wong CY, Baldelli A, Hoyos CM, Tietz O, Ong HX, Traini D. Insulin delivery to the brain via the nasal route: unraveling the potential for Alzheimer's disease therapy. Drug delivery and translational research. 2024 Jul;14(7):1776-93.
49. Chen J, Hu L, Yang G, Hu Q. Current therapeutic strategy in the nasal delivery of insulin: recent advances and future directions. Current Pharmaceutical Biotechnology. 2018 Apr 1;19(5):400-15.
50. Chen X, Wang L, Yu H, Li C, Feng J, Haq F, Khan A, Khan RU. Preparation, properties and challenges of the microneedles-based insulin delivery system. Journal of Controlled Release. 2018 Oct 28;288:173-88.
51. Lum JW, Bailey RJ, Barnes-Lomen V, Naranjo D, Hood KK, Lal RA, Arbiter B, Brown AS, DeSalvo DJ, Pettus J, Calhoun P. A real-world prospective study of the safety and effectiveness of the loop open source automated insulin delivery system. Diabetes technology & therapeutics. 2021 May;23(5):367-75.

52. Karol AB, O'Malley G, Fallurin R, Levy CJ. Automated insulin delivery systems as a treatment for type 2 diabetes mellitus: a review. Endocrine Practice. 2023 Mar 1;29(3):214-20.
53. Wang M, Wang C, Ren S, Pan J, Wang Y, Shen Y, Zeng Z, Cui H, Zhao X. Versatile oral insulin delivery nanosystems: from materials to nanostructures. International journal of molecular sciences. 2022 Mar 20;23(6):3362.
54. Gedawy A, Martinez J, Al-Salami H, Dass CR. Oral insulin delivery: existing barriers and current counter-strategies. Journal of pharmacy and pharmacology. 2018 Feb;70(2):197-213.
55. Oliver N, Reddy M, Marriott C, Walker T, Heinemann L. Open source automated insulin delivery: addressing the challenge. NPJ digital medicine. 2019 Dec 11;2(1):124.