Nanocarrier Based Drug Delivery Systems for Improved Management of Diabetes Mellitus

Mehak gupta[1*]. Achla Sharma[2]

[1*] *SIRDA Polytechnic, Sunder Nagar at Naulakha, P.O. – Kanaid, Distt. Mandi, Himachal Pradesh, PIN code – 175019, India.*

[2] *Minerva College of Pharmacy, Minerva groups of Colleges, Indora, Himachal Pradesh PIN code – 176401, India.*

***Corresponding Author:**

Miss. Mehak gupta

SIRDA Polytechnic, Sunder Nagar at Naulakha, P.O. – Kanaid, Distt. Mandi, Himachal Pradesh, PIN code – 175019, India.

Email; mehakgupta4008@gmail.com

Abstract

Nanocarrier-based drug delivery systems have emerged as a promising strategy for improving the management of diabetes mellitus by addressing the limitations associated with conventional therapeutic approaches. Diabetes, a chronic metabolic disorder characterized by persistent hyperglycemia, requires long-term treatment strategies that often suffer from poor bioavailability, frequent dosing, systemic side effects, and low patient compliance. Nanotechnology offers innovative solutions through the development of advanced delivery platforms such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, dendrimers, and nanoemulsions. These nanocarriers enhance drug stability, protect labile molecules like insulin from enzymatic degradation, and facilitate controlled and targeted drug delivery. In particular, nanocarrier systems enable alternative administration routes, including oral, nasal, and transdermal delivery, thereby improving patient adherence and therapeutic outcomes. Furthermore, the integration of smart and stimuli-responsive nanocarriers, including glucose-responsive systems, allows for self-regulated drug release that closely mimics physiological insulin secretion. Despite significant progress in preclinical research, challenges related to safety, toxicity, large-scale manufacturing, and regulatory approval continue to hinder clinical translation. Ongoing advancements in nanomedicine, along with the incorporation of personalized therapy and artificial intelligence, are expected to further enhance the efficacy and precision of diabetes treatment. This review comprehensively highlights the role of nanocarriers in diabetes management, emphasizing their potential to overcome existing therapeutic barriers and improve long-term disease control.

Keywords: Nanocarriers, Diabetes mellitus, Targeted drug delivery, Insulin delivery, Controlled release, Bioavailability enhancement.

1. Introduction

1.1 Diabetes Mellitus: An Overview

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels resulting from impaired insulin secretion, insulin resistance, or both. It is broadly classified into Type 1 diabetes mellitus (T1DM), which is caused by autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency, and Type 2 diabetes mellitus (T2DM), which is associated with insulin resistance and relative insulin deficiency [1]. The global prevalence of diabetes has increased significantly due to sedentary lifestyles, unhealthy dietary patterns, and aging populations. Persistent hyperglycemia in diabetes is linked with severe long-term complications, including microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular complications like cardiovascular diseases and stroke. Therefore, maintaining optimal glycemic control is essential to prevent disease progression and associated complications [2].

1.2 Limitations of Conventional Therapy

Conventional diabetes management primarily relies on insulin injections and oral hypoglycemic agents such as metformin, sulfonylureas, and other classes of drugs. Although these therapies are effective in controlling blood glucose levels, they are associated with several limitations. Insulin therapy often requires frequent subcutaneous injections, which can lead to poor patient compliance and discomfort [3]. Many oral antidiabetic drugs suffer from low bioavailability, rapid metabolism, and non-specific distribution in the body. Additionally, these therapies may cause adverse effects such as hypoglycemia, gastrointestinal disturbances, and weight gain. Another major limitation is their inability to mimic the physiological pattern of insulin secretion, resulting in suboptimal glycemic control. These challenges highlight the need for improved drug delivery approaches that can enhance therapeutic efficiency and patient adherence [4].

1.3 Need for Targeted Drug Delivery

Targeted drug delivery systems have gained considerable attention as they aim to deliver therapeutic agents directly to the site of action while minimizing systemic exposure. In the context of diabetes, targeted delivery is crucial for improving drug efficacy and reducing side effects [5]. Such systems can enhance the delivery of insulin and other antidiabetic agents to specific organs such as the liver, pancreas, or muscle tissues, where glucose metabolism is actively regulated. Moreover, targeted delivery can protect sensitive biomolecules like insulin from enzymatic degradation, particularly in non-invasive routes such as oral administration. By enabling controlled and sustained drug release, these systems can reduce dosing frequency and improve patient compliance. Overall, targeted drug delivery offers a promising strategy to overcome the shortcomings of conventional therapies [6].

1.4 Role of Nanocarriers in Diabetes Management

Nanocarriers have emerged as advanced drug delivery platforms that can significantly improve the management of diabetes mellitus. These nanoscale systems, including polymeric nanoparticles, liposomes, micelles, dendrimers, and solid lipid nanoparticles, provide unique advantages due to their small size and modifiable surface properties [7]. Nanocarriers can encapsulate both hydrophilic and hydrophobic drugs, protecting them from degradation and enhancing their stability. They also facilitate improved drug absorption and bioavailability, particularly for peptide-based drugs like insulin. Furthermore, nanocarriers can be engineered for controlled and sustained drug release, thereby maintaining consistent therapeutic levels over extended periods. Surface functionalization enables targeted delivery to specific tissues or cells, reducing off-target effects. Recent developments have also introduced glucose-responsive nanocarriers that release insulin in response to blood glucose levels, offering a more physiological approach to diabetes treatment [8].

1.5 Scope of the Review

The present review focuses on the exploration of nanocarrier-based drug delivery systems as a novel approach for the improved management of diabetes mellitus. It aims to provide a detailed discussion of various nanocarrier systems, their design principles, mechanisms of drug delivery, and their therapeutic potential [9]. The review also highlights recent advancements in the field, including smart and stimuli-responsive nanocarriers, along with their preclinical and clinical evaluations. Additionally, challenges related to safety, scalability, regulatory approval, and clinical translation are addressed. By integrating current knowledge and research developments, this review seeks to offer insights into the future prospects of nanotechnology-driven strategies for more effective and patient-friendly diabetes management [10].

2. Pathophysiology of Diabetes Mellitus

2.1 Type 1 Diabetes

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the selective destruction of insulin-producing β-cells in the pancreatic islets of Langerhans. This process is primarily mediated by autoreactive T lymphocytes, which target β-cell antigens, leading to progressive cell loss and absolute insulin deficiency [11]. Genetic susceptibility, particularly involving human leukocyte antigen (HLA) genes, along with environmental triggers such as viral infections, are believed to contribute to disease onset. As β-cell mass declines, the body loses its ability to regulate blood glucose levels, resulting in persistent hyperglycemia. Patients with T1DM require lifelong exogenous insulin therapy to maintain metabolic homeostasis and prevent acute complications such as diabetic ketoacidosis [12].

2.2 Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder characterized by a combination of insulin resistance and relative insulin deficiency. Unlike T1DM, T2DM develops gradually and is strongly associated with genetic predisposition, obesity, sedentary lifestyle, and aging [13]. In the early stages, pancreatic β-cells compensate for insulin resistance by increasing insulin secretion; however, over time, this compensatory mechanism fails, leading to impaired glucose regulation. Chronic hyperglycemia further exacerbates metabolic disturbances, including dyslipidemia and inflammation. T2DM is the most prevalent form of diabetes and is often associated with comorbidities such as hypertension and cardiovascular disease [14].

2.3 Insulin Resistance

Insulin resistance is a key pathological feature of Type 2 diabetes and refers to the reduced responsiveness of peripheral tissues primarily skeletal muscle, adipose tissue, and the liver to insulin. Under normal conditions, insulin facilitates glucose uptake in muscle and adipose tissues and suppresses hepatic glucose production [15]. However, in insulin-resistant states, these processes are impaired, leading to decreased glucose uptake and increased endogenous glucose production. Molecular mechanisms underlying insulin resistance include defects in insulin receptor signalling pathways, increased levels of free fatty acids, chronic low-grade inflammation, and oxidative stress. As a result, higher levels of insulin are required to achieve normal glucose homeostasis, placing additional stress on pancreatic β-cells [16].

2.4 β-Cell Dysfunction

β-cell dysfunction plays a central role in the progression of both Type 1 and Type 2 diabetes. In T1DM, β-cell loss is primarily due to autoimmune destruction, whereas in T2DM, dysfunction results from chronic metabolic stress. Prolonged exposure to high glucose (glucotoxicity) and elevated free fatty acids (lipotoxicity) impairs β-cell function and reduces insulin secretion [17]. Additionally, oxidative stress, endoplasmic reticulum stress, and inflammatory cytokines contribute to β-cell apoptosis and decreased regenerative capacity. As β-cell function deteriorates, insulin secretion becomes insufficient to compensate for insulin resistance, leading to worsening hyperglycemia and disease progression [18].

2.5 Chronic Complications

Chronic complications of diabetes arise from prolonged hyperglycemia and are a major cause of morbidity and mortality. These complications are broadly classified into microvascular and macrovascular disorders. Microvascular complications include diabetic retinopathy, nephropathy, and neuropathy, which result from damage to small blood vessels. Macrovascular complications involve large blood vessels and include cardiovascular diseases such as coronary artery disease, stroke, and peripheral arterial disease [19]. The underlying mechanisms involve advanced glycation end-products (AGEs), oxidative stress,

inflammation, and endothelial dysfunction. Persistent hyperglycemia triggers these pathways, leading to structural and functional damage in various organs. Effective glycemic control and early intervention are essential to prevent or delay the onset of these complications [20].

3. Challenges in Conventional Antidiabetic Therapy

Poor bioavailability remains one of the most critical limitations of conventional antidiabetic therapies, particularly for peptide- and protein-based drugs such as insulin, glucagon-like peptide-1 (GLP-1) analogs, and other biologics. When administered via the oral route, these macromolecules encounter multiple physiological barriers, including the acidic environment of the stomach, proteolytic enzymes in the gastrointestinal tract (such as pepsin, trypsin, and chymotrypsin), and the epithelial barrier of the intestinal mucosa [21]. These factors collectively lead to extensive degradation and minimal absorption of the active drug into systemic circulation. Additionally, even small-molecule oral antidiabetic drugs may exhibit poor solubility and permeability, resulting in variable absorption profiles. First-pass hepatic metabolism further reduces the fraction of the drug reaching systemic circulation in an active form [22]. Consequently, higher doses are often required to achieve therapeutic efficacy, which may increase interpatient variability and the risk of dose-related adverse effects. This inherent limitation significantly compromises treatment efficiency and highlights the urgent need for advanced delivery strategies that can enhance drug stability, permeability, and overall bioavailability [23].

Frequent dosing is another major drawback associated with conventional diabetes management strategies. Many antidiabetic agents, including insulin and certain oral hypoglycemic drugs, possess relatively short biological half-lives, necessitating multiple daily administrations to maintain effective glycemic control. In the case of insulin therapy, patients often require several subcutaneous injections per day, including basal and bolus doses, to mimic physiological insulin secretion. This complex dosing regimen not only increases the treatment burden but also introduces variability in drug absorption depending on the site and timing of injection [24]. Similarly, oral medications may require two or three doses per day to sustain therapeutic plasma concentrations. Such frequent dosing schedules can be inconvenient, especially for elderly patients or those with busy lifestyles, leading to missed doses or incorrect administration. Inconsistent dosing can result in fluctuations in blood glucose levels, increasing the risk of both hyperglycemia and hypoglycemia. Therefore, reducing dosing frequency through sustained and controlled drug delivery systems is a key objective in improving diabetes management [25].

Systemic side effects represent a significant concern in conventional antidiabetic therapy due to the non-specific distribution of drugs throughout the body. Since most traditional drug delivery approaches lack targeting capability, therapeutic agents act not only at the intended site but also on non-target tissues, leading to undesirable effects [26]. Hypoglycemia is one of the most serious and common adverse effects, particularly associated with insulin and insulin secretagogues such as sulfonylureas. Gastrointestinal disturbances, including nausea, vomiting, diarrhea, and abdominal discomfort, are frequently observed with drugs like

metformin and GLP-1 receptor agonists. Additionally, certain classes of drugs, such as thiazolidinediones, are linked with weight gain, fluid retention, and increased risk of heart failure. Long-term use of some antidiabetic medications may also contribute to hepatic or renal complications. These side effects can negatively impact patient quality of life and may necessitate dose adjustments or discontinuation of therapy. The inability to precisely control drug distribution and release underscores the need for targeted delivery systems that can minimize systemic exposure and enhance therapeutic specificity [26].

Low patient compliance is a multifactorial challenge that significantly affects the success of conventional antidiabetic therapy. The chronic nature of diabetes requires lifelong management, often involving complex treatment regimens that include multiple medications, frequent dosing, and regular monitoring of blood glucose levels. Insulin therapy, in particular, poses challenges due to the need for repeated injections, which can cause pain, discomfort, and psychological distress, including needle phobia [27]. Furthermore, strict adherence to dietary restrictions, physical activity recommendations, and medication schedules can be difficult to maintain over extended periods. Socioeconomic factors, lack of patient education, and limited access to healthcare resources may further contribute to poor adherence. Fear of adverse effects such as hypoglycemia also discourages patients from following prescribed regimens consistently. As a result, suboptimal compliance leads to poor glycemic control, increasing the risk of disease progression and complications. Improving patient-friendly drug delivery systems, such as non-invasive and long-acting formulations, is essential to enhance adherence and overall therapeutic outcomes [28].

Drug degradation is a critical issue, particularly for biologically derived antidiabetic agents such as insulin, peptides, and protein-based therapeutics. These molecules are inherently unstable and highly susceptible to physical, chemical, and enzymatic degradation. In the gastrointestinal tract, enzymatic activity rapidly breaks down peptide drugs, rendering them inactive before they can be absorbed [29]. Even during storage and handling, factors such as temperature fluctuations, exposure to light, oxidation, and pH variations can compromise drug stability. For example, insulin formulations require strict storage conditions to maintain their structural integrity and biological activity. Additionally, aggregation or denaturation of protein-based drugs can reduce efficacy and potentially trigger immunogenic responses. Conventional delivery systems often fail to provide adequate protection against these degradative processes, leading to reduced therapeutic effectiveness and shorter shelf life. Therefore, there is a pressing need for advanced drug delivery approaches, such as encapsulation within protective carriers, to enhance drug stability, prolong activity, and ensure consistent therapeutic performance [30].

4. Nanocarrier-Based Drug Delivery Systems

Nanocarriers are nanoscale drug delivery systems typically ranging in size from 1 to 1000 nm, designed to transport therapeutic agents to specific sites in the body in a controlled and efficient manner. These carriers are engineered using a variety of materials, including polymers, lipids, and surfactants, and can encapsulate, adsorb, or conjugate drugs within their

structure [31]. The unique physicochemical properties of nanocarriers, such as high surface area-to-volume ratio, tunable surface characteristics, and the ability to cross biological barriers, make them highly suitable for drug delivery applications. In the context of diabetes, nanocarriers play a crucial role in improving the stability and delivery of sensitive biomolecules like insulin, enhancing their therapeutic efficacy while minimizing degradation and systemic loss [32].

4.2 Advantages of Nanotechnology in Diabetes

Nanotechnology offers numerous advantages in the management of diabetes mellitus by addressing the limitations associated with conventional therapies. One of the key benefits is the protection of labile drugs, such as insulin and peptide-based therapeutics, from enzymatic degradation in biological environments [33]. Nanocarriers can enhance drug solubility and bioavailability, allowing for more efficient absorption and reduced dosing requirements. Additionally, these systems enable controlled and sustained drug release, maintaining stable blood glucose levels over extended periods and reducing the frequency of administration. Surface modification of nanocarriers allows for targeted delivery to specific tissues or cells, thereby improving therapeutic precision and minimizing off-target effects [34]. Furthermore, nanotechnology facilitates the development of non-invasive delivery routes, such as oral, nasal, and transdermal systems, which significantly improve patient compliance. Emerging smart nanocarriers, including glucose-responsive systems, can further revolutionize diabetes treatment by enabling self-regulated drug release in response to physiological conditions [35].

4.3 Mechanism of Targeted Delivery

The mechanism of targeted drug delivery using nanocarriers involves both passive and active targeting strategies. Passive targeting primarily relies on the physicochemical properties of nanocarriers, such as size, shape, and surface charge, which influence their distribution and accumulation in specific tissues. In certain pathological conditions, enhanced permeability and retention (EPR) effects allow nanocarriers to preferentially accumulate in target tissues [36]. Active targeting, on the other hand, involves the functionalization of nanocarrier surfaces with specific ligands such as antibodies, peptides, or small molecules that can recognize and bind to receptors expressed on target cells. In diabetes management, such targeting strategies can be used to direct drugs toward pancreatic β-cells, liver cells, or insulin-sensitive tissues. Upon reaching the target site, nanocarriers can release their payload in a controlled manner through diffusion, degradation, or stimuli-responsive mechanisms such as pH, enzymes, or glucose levels. This precise delivery enhances therapeutic efficacy while reducing systemic exposure and side effects [37].

Polymeric nanoparticles are one of the most extensively studied nanocarrier systems for drug delivery applications. They are typically prepared using biodegradable and biocompatible polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and alginate. These nanoparticles can encapsulate drugs within their matrix or adsorb them onto their surface, providing protection against degradation and enabling controlled drug release [38]. In

diabetes management, polymeric nanoparticles are particularly useful for oral insulin delivery, as they can enhance mucosal adhesion and facilitate transport across intestinal barriers. Additionally, their surface can be modified with targeting ligands to improve site-specific delivery. Their versatility, stability, and ability to provide sustained release make them highly promising for long-term glycaemic control [39].

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Due to their amphiphilic nature, liposomes can encapsulate both hydrophilic drugs (in the aqueous core) and hydrophobic drugs (within the lipid bilayer). This dual-loading capability makes them highly versatile drug delivery systems [40]. In diabetes treatment, liposomes have been explored for insulin delivery through various routes, including oral, transdermal, and pulmonary administration. They provide protection against enzymatic degradation and can be engineered for controlled release. Furthermore, surface modification with polyethylene glycol (PEGylation) or targeting ligands enhances their circulation time and targeting efficiency. However, challenges such as stability, leakage, and large-scale production need to be addressed for widespread clinical application [41].

Solid lipid nanoparticles (SLNs) are composed of solid lipids that remain in a solid state at both room and body temperatures, stabilized by surfactants. These carriers combine the advantages of traditional lipid-based systems with improved stability and controlled drug release properties [42]. SLNs provide protection for encapsulated drugs against chemical and enzymatic degradation and enhance bioavailability. In diabetes management, SLNs have shown potential for delivering insulin and oral hypoglycemic agents with improved stability and sustained release profiles. Their biocompatibility and low toxicity make them attractive candidates; however, limitations such as limited drug loading capacity and potential drug expulsion during storage need to be considered [43].

Nanostructured lipid carriers (NLCs) are an advanced generation of lipid nanoparticles that consist of a mixture of solid and liquid lipids, resulting in a less ordered lipid matrix. This structural modification overcomes the limitations of SLNs by improving drug loading capacity and reducing drug expulsion during storage. NLCs provide enhanced stability, controlled release, and better bioavailability of encapsulated drugs. In the context of diabetes, NLCs have been investigated for oral and transdermal delivery of insulin and other antidiabetic agents. Their ability to incorporate higher drug quantities and maintain long-term stability makes them a promising platform for sustained and targeted drug delivery [44].

Dendrimers are highly branched, tree-like polymeric nanostructures with a well-defined architecture consisting of a core, repeating branches and terminal functional groups. Their unique structure provides a high degree of surface functionality, allowing multiple drug molecules to be attached or encapsulated simultaneously [42]. Dendrimers exhibit excellent solubility, controlled size, and the ability to precisely tailor their surface properties for targeted delivery. In diabetes management, dendrimers have been explored for enhancing the delivery of insulin and oral antidiabetic drugs. Their multivalency enables the attachment of

targeting ligands, improving specificity toward particular tissues or cells. However, concerns regarding cytotoxicity and biocompatibility need to be carefully addressed [45].

Nanoemulsions are thermodynamically stable or metastable colloidal systems consisting of nanosized droplets of one liquid dispersed within another immiscible liquid, typically oil-in-water or water-in-oil systems, stabilized by surfactants. Their small droplet size enhances drug solubility, absorption, and bioavailability. In diabetes treatment, nanoemulsions have been widely investigated for improving the oral delivery of poorly soluble antidiabetic drugs and for enhancing the stability of insulin formulations. They also facilitate alternative routes of administration, including transdermal and nasal delivery. Nanoemulsions offer advantages such as ease of preparation, high drug loading capacity, and improved pharmacokinetic profiles. However, issues related to long-term stability and surfactant toxicity must be considered during formulation development [46].

Table 1: Types of Nanocarriers Used in Diabetes Drug Delivery and Their Advantages

Sr. No.	Nanocarrier	Drug Used	Advantages	Reference
1	Polymeric nanoparticles	Insulin	Enhanced stability, controlled release, improved oral bioavailability	[47]
2	Polymeric nanoparticles	Metformin	Sustained release, reduced dosing frequency	[48]
3	Liposomes	Insulin	Protection from enzymatic degradation, biocompatibility	[49]
4	Liposomes	GLP-1 analogs	Improved circulation time, targeted delivery	[50]
5	Solid lipid nanoparticles	Insulin	Enhanced stability, controlled release, low toxicity	[51]
6	Solid lipid nanoparticles	Glibenclamide	Improved bioavailability, reduced side effects	[52]
7	Nanostructured lipid carriers	Insulin	High drug loading, improved stability, sustained release	[53]
8	Nanostructured lipid carriers	Pioglitazone	Enhanced permeability, reduced systemic toxicity	[54]
9	Dendrimers	Insulin	Targeted delivery, high drug loading capacity	[55]
10	Dendrimers	Metformin	Improved solubility, controlled drug release	[56]
11	Nanoemulsions	Insulin	Improved absorption, non-invasive delivery	[57]
12	Nanoemulsions	Glipizide	Enhanced solubility, increased bioavailability	[58]

13	Polymeric micelles	Repaglinide	Improved solubility, prolonged circulation	[59]
14	Chitosan nanoparticles	Insulin	Mucoadhesion, enhanced intestinal absorption	[60]
15	Gold nanoparticles	Insulin	Targeted delivery, improved cellular uptake	[61]

5. Nanocarriers for Insulin Delivery

Oral delivery of insulin has long been considered a highly desirable alternative to conventional subcutaneous injections due to its non-invasive nature and improved patient compliance. However, the oral route presents significant challenges, including enzymatic degradation in the gastrointestinal tract and poor permeability across the intestinal epithelium. Nanocarrier-based systems have emerged as promising solutions to overcome these barriers [62]. Polymeric nanoparticles, liposomes, and lipid-based carriers can encapsulate insulin, protecting it from acidic pH and proteolytic enzymes. Additionally, surface modifications using mucoadhesive polymers such as chitosan enhance residence time in the intestinal mucosa and promote paracellular transport. Some advanced systems incorporate permeation enhancers or enzyme inhibitors to further improve absorption. These strategies enable improved bioavailability and facilitate insulin transport into systemic circulation, mimicking the physiological pathway of endogenous insulin via the portal vein to the liver [63].

Nasal delivery of insulin offers a non-invasive and rapid route for systemic drug absorption due to the highly vascularized nasal mucosa and avoidance of first-pass metabolism. Nanocarriers play a crucial role in enhancing the efficiency of this delivery route by improving drug stability and residence time within the nasal cavity. Formulations such as nanoemulsions, polymeric nanoparticles, and liposomes can encapsulate insulin and protect it from enzymatic degradation present in nasal secretions [64]. Mucoadhesive nanocarriers further enhance contact with the nasal epithelium, facilitating improved absorption. Additionally, nanosystems can transiently open tight junctions between epithelial cells, allowing for enhanced paracellular transport of insulin. Despite these advantages, challenges such as limited dosing volume, mucociliary clearance, and potential nasal irritation must be carefully addressed to optimize therapeutic outcomes [65].

Transdermal delivery of insulin represents another attractive non-invasive approach, aiming to deliver insulin across the skin into systemic circulation. However, the stratum corneum, the outermost layer of the skin, acts as a significant barrier to the penetration of large molecules like insulin. Nanocarriers such as lipid nanoparticles, nanoemulsions, and polymeric nanoparticles have been investigated to enhance skin permeability [66]. These systems can facilitate drug transport through hair follicles, sweat glands, or disrupted skin layers. Advanced approaches, including microneedle-assisted nanocarrier delivery and iontophoresis, further improve transdermal insulin absorption. Nanocarriers can also provide controlled and sustained release, maintaining stable blood glucose levels over extended

periods. This method significantly reduces the need for injections and enhances patient comfort, although challenges related to skin irritation and variable permeability remain [67].

Injectable nanoformulations represent an advancement over conventional insulin injections by improving pharmacokinetics and reducing dosing frequency. Nanocarriers such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles can be administered via subcutaneous or intravenous routes to provide sustained and controlled release of insulin [68]. These formulations protect insulin from rapid degradation and clearance, thereby prolonging its circulation time and maintaining consistent therapeutic levels. Additionally, surface-modified nanocarriers can enhance tissue targeting and reduce variability in absorption. Long-acting nanoformulations are particularly beneficial in reducing the frequency of injections, thereby improving patient compliance. Furthermore, these systems can be designed to mimic physiological insulin release patterns more closely than traditional formulations, leading to better glycemic control [69].

Glucose-responsive nanocarrier systems represent a significant advancement toward achieving self-regulated insulin delivery, often referred to as “smart” drug delivery. These systems are designed to release insulin in response to changes in blood glucose levels, thereby closely mimicking the natural function of pancreatic β-cells. Various mechanisms have been explored, including glucose oxidase-based systems, phenylboronic acid-based sensors, and enzyme-triggered release systems [70]. In these formulations, nanocarriers remain stable under normoglycemic conditions but undergo structural or chemical changes in hyperglycemic states, triggering insulin release. This approach minimizes the risk of hypoglycemia and eliminates the need for frequent monitoring and dosing adjustments. Although still largely in the experimental stage, glucose-responsive nanocarriers hold immense potential for revolutionizing diabetes management by providing automated and precise glycemic control [71].

6. Nanocarriers for Oral Antidiabetic Drugs

6.1 Metformin

Metformin is the first-line oral antidiabetic drug widely used for the management of Type 2 diabetes mellitus due to its efficacy in reducing hepatic glucose production and improving insulin sensitivity. However, its conventional formulation is associated with limitations such as incomplete absorption, gastrointestinal side effects, and the need for frequent dosing due to its relatively short half-life. Nanocarrier-based delivery systems, including polymeric nanoparticles, liposomes, and solid lipid nanoparticles, have been investigated to overcome these challenges [72]. Encapsulation of metformin within nanocarriers enhances its bioavailability by improving intestinal permeability and protecting it from premature degradation. Additionally, these systems enable controlled and sustained drug release, which helps maintain consistent plasma drug levels and reduces dosing frequency. Targeted delivery approaches may further improve therapeutic efficacy while minimizing gastrointestinal irritation, thereby enhancing patient tolerance and compliance [73].

6.2 Sulfonylureas

Sulfonylureas, such as glibenclamide and glipizide, are commonly prescribed insulin secretagogues that stimulate pancreatic β-cells to release insulin. Despite their effectiveness, they are associated with risks such as hypoglycemia, weight gain, and variable pharmacokinetics. Nanocarrier-based formulations have been explored to improve the therapeutic profile of sulfonylureas by enhancing drug solubility, stability, and targeted delivery. Lipid-based nanocarriers, including solid lipid nanoparticles and nanoemulsions, can increase the dissolution rate of poorly water-soluble sulfonylureas, thereby improving their bioavailability. Controlled release from nanocarriers helps maintain stable drug concentrations, reducing the risk of sudden hypoglycemic episodes. Furthermore, targeted delivery systems can potentially direct the drug toward pancreatic tissues, improving efficacy while minimizing systemic exposure and associated side effects [74].

6.3 GLP-1 Analogs

Glucagon-like peptide-1 (GLP-1) analogs are an important class of antidiabetic agents that enhance glucose-dependent insulin secretion, suppress glucagon release, and slow gastric emptying. However, these peptide-based drugs are highly susceptible to enzymatic degradation in the gastrointestinal tract, limiting their oral bioavailability and necessitating parenteral administration. Nanocarrier systems offer a promising strategy to enable oral delivery of GLP-1 analogs [75]. Polymeric nanoparticles, liposomes, and dendrimers can encapsulate these peptides, protecting them from enzymatic degradation and facilitating their transport across the intestinal epithelium. Surface modification with mucoadhesive and permeation-enhancing agents further improves absorption. Additionally, nanocarriers can provide sustained release profiles, prolonging the pharmacological action of GLP-1 analogs and reducing dosing frequency. These advancements have the potential to significantly improve patient compliance and expand the clinical utility of GLP-1–based therapies [72].

6.4 DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin and vildagliptin, function by preventing the degradation of incretin hormones, thereby enhancing insulin secretion and reducing blood glucose levels. Although these drugs generally exhibit good oral bioavailability, they may still face challenges such as rapid clearance and the need for consistent plasma levels to maintain efficacy [76]. Nanocarrier-based delivery systems can further optimize the pharmacokinetic and pharmacodynamic profiles of DPP-4 inhibitors. Encapsulation within nanoparticles or lipid-based carriers allows for sustained and controlled drug release, ensuring prolonged therapeutic action and reduced dosing frequency. Additionally, nanocarriers can facilitate targeted delivery to specific tissues, potentially improving drug efficiency and minimizing off-target effects. Such approaches can enhance the overall effectiveness of DPP-4 inhibitors in long-term diabetes management [77].

6.5 Herbal Antidiabetic Compounds

Herbal antidiabetic compounds, derived from natural sources such as plants, have gained significant attention due to their potential therapeutic benefits and lower side effect profiles. Bioactive compounds such as curcumin, berberine, quercetin, and resveratrol exhibit antidiabetic properties through mechanisms including antioxidant activity, improved insulin sensitivity, and modulation of glucose metabolism. However, many of these compounds suffer from poor solubility, low stability, and limited bioavailability, which restrict their clinical application [78]. Nanocarrier-based systems provide an effective platform to overcome these limitations by enhancing solubility, protecting against degradation, and improving absorption. Polymeric nanoparticles, nanoemulsions, and lipid-based carriers have been successfully used to deliver herbal compounds with improved pharmacokinetic profiles. Additionally, controlled and targeted delivery of these bioactives can enhance their therapeutic efficacy while reducing required doses. The integration of nanotechnology with herbal medicine represents a promising approach for the development of safer and more effective antidiabetic therapies [79].

7. Targeted and Smart Nanocarriers in Diabetes

Glucose-responsive nanoparticles represent a highly advanced and intelligent approach in diabetes therapy, designed to mimic the physiological function of pancreatic β-cells by releasing insulin in response to elevated blood glucose levels. These systems are typically engineered using glucose-sensitive components such as glucose oxidase, phenylboronic acid derivatives, or concanavalin A, which can detect fluctuations in glucose concentration [7]. Upon exposure to hyperglycaemic conditions, biochemical or structural changes occur within the nanocarrier, triggering the controlled release of insulin. For instance, glucose oxidase-based systems convert glucose into gluconic acid, leading to a local pH change that destabilizes the carrier and releases the drug. This self-regulated mechanism helps maintain normoglycemia while minimizing the risk of hypoglycemia, a common complication of conventional insulin therapy. Such smart systems reduce the need for frequent monitoring and dosing adjustments, thereby improving patient convenience and therapeutic precision, although challenges related to long-term stability and biocompatibility remain under investigation [80].

Stimuli-responsive nanocarriers, also known as “smart” delivery systems, are designed to release therapeutic agents in response to specific internal or external stimuli. These stimuli may include pH variations, temperature changes, enzymatic activity, redox conditions, or external triggers such as magnetic fields and ultrasound. In the context of diabetes, pH- and enzyme-responsive systems are particularly relevant due to the metabolic changes associated with hyperglycemia. For example, pH-sensitive nanocarriers can release insulin in response to the acidic microenvironment generated by glucose metabolism [81]. Similarly, enzyme-responsive systems can be activated by enzymes that are upregulated in diabetic conditions. External stimuli-responsive systems, such as magnetically guided nanoparticles, offer additional control over drug localization and release. These systems enable precise

spatiotemporal control of drug delivery, enhancing therapeutic efficacy while reducing systemic exposure and side effects. However, the complexity of their design and the need for precise triggering mechanisms pose challenges for clinical translation [82].

Ligand-targeted nanocarrier systems are designed to achieve site-specific drug delivery by functionalizing the surface of nanoparticles with ligands that can selectively bind to receptors expressed on target cells or tissues [83]. In diabetes management, this approach can be utilized to direct therapeutic agents toward insulin-sensitive tissues such as the liver, skeletal muscle, or adipose tissue, as well as pancreatic β-cells. Common targeting ligands include antibodies, peptides, aptamers, and small molecules such as folic acid or transferrin [84]. Upon binding to specific receptors, the nanocarriers are internalized via receptor-mediated endocytosis, allowing efficient intracellular drug delivery. This targeted approach enhances drug accumulation at the desired site while minimizing off-target distribution and systemic side effects. Additionally, ligand-targeted systems can improve the efficacy of lower drug doses, thereby reducing toxicity. Despite their promising potential, issues such as ligand stability, immunogenicity, and large-scale manufacturing remain important considerations [85].

Controlled release nanocarrier systems are designed to deliver drugs at a predetermined rate over an extended period, maintaining therapeutic drug concentrations within the desired range. These systems are particularly beneficial in diabetes management, where maintaining stable blood glucose levels is critical [86]. Nanocarriers such as polymeric nanoparticles, lipid-based systems, and hydrogels can be engineered to release drugs through mechanisms such as diffusion, degradation, or swelling. By providing sustained drug release, these systems reduce the need for frequent dosing and minimize fluctuations in plasma drug levels, thereby lowering the risk of hypoglycemia and hyperglycemia. Advanced controlled release systems can also be integrated with stimuli-responsive or targeting features, enabling more precise and personalized therapy. Overall, controlled release nanocarriers contribute to improved therapeutic outcomes, enhanced patient compliance, and better long-term management of diabetes [87].

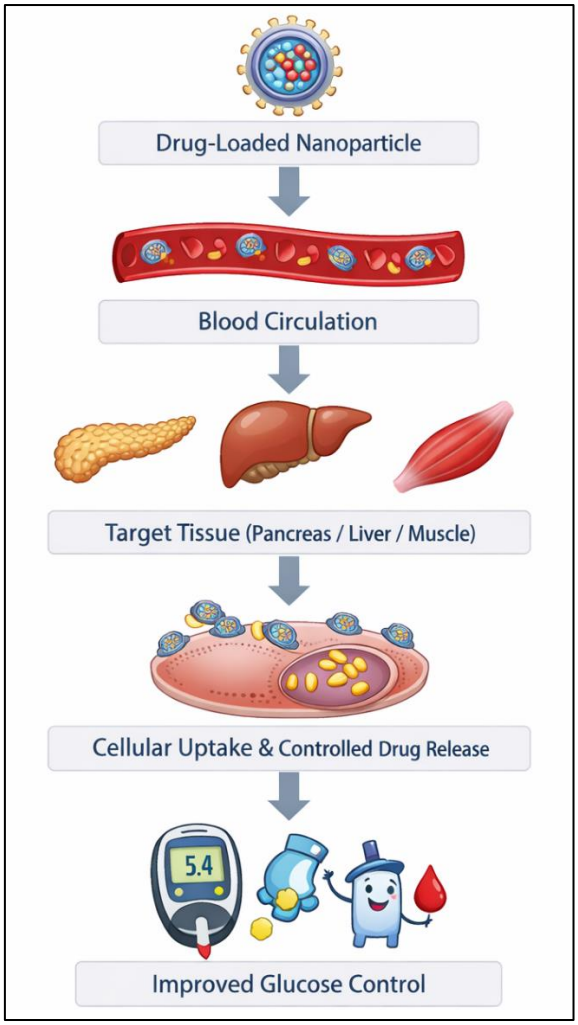

Figure 1: Mechanism of nanocarrier based targeted drug delivery in diabetes mellitus

8. Safety, Toxicity and Regulatory Considerations

Biocompatibility is a fundamental requirement for the successful application of nanocarrier-based drug delivery systems in diabetes management. It refers to the ability of a material to perform its intended function without eliciting any undesirable local or systemic effects in the body. Nanocarriers intended for clinical use must be composed of materials that are non-toxic, non-immunogenic, and biodegradable into safe byproducts [88]. Commonly used materials such as poly(lactic-co-glycolic acid) (PLGA), chitosan, lipids, and albumin have demonstrated favorable biocompatibility profiles. Surface properties, particle size, charge, and hydrophobicity significantly influence the interaction of nanocarriers with biological systems, including cellular uptake, circulation time, and immune recognition. Poorly designed nanocarriers may trigger immune responses, protein adsorption (opsonization), or rapid clearance by the reticuloendothelial system. Therefore, careful optimization of physicochemical characteristics and thorough in vitro and in vivo evaluations are essential to ensure safe and effective clinical application [89].

Despite their promising advantages, nanocarriers may pose potential toxicity risks that must be carefully evaluated. Toxicity can arise from the core material, surface coatings, degradation products, or residual solvents used during formulation. Nanoparticles may induce oxidative stress, inflammation, or cellular damage depending on their size, shape, and composition. For instance, certain inorganic nanoparticles, such as metallic or carbon-based systems, have been associated with cytotoxicity and accumulation in vital organs like the liver, kidneys, and lungs [90]. Additionally, long-term exposure to nanoparticles may lead to unforeseen chronic effects, including immunogenicity or genotoxicity. The small size of nanocarriers allows them to cross biological barriers, including the blood–brain barrier, raising concerns about unintended distribution and toxicity. Dose-dependent toxicity and accumulation with repeated administration are also critical considerations, particularly in chronic diseases like diabetes that require long-term treatment. Comprehensive toxicological studies, including acute, sub-chronic, and chronic evaluations, are therefore necessary to establish safety profiles [91].

The regulatory approval of nanocarrier-based drug delivery systems presents significant challenges due to their complex nature and lack of standardized evaluation frameworks. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require extensive data on the safety, efficacy, quality, and manufacturing consistency of nanomedicines [92]. However, conventional regulatory guidelines are often not fully applicable to nanoscale systems, as their behavior can differ significantly from traditional formulations. Critical issues include characterization of particle size distribution, surface properties, drug loading efficiency, and release kinetics. Additionally, reproducibility and scalability of manufacturing processes remain major concerns. The absence of universally accepted standards for nanotoxicology and quality control further complicates the approval process. Regulatory authorities are increasingly working toward developing specific guidelines for nanomedicines, but harmonization across regions is still evolving. Addressing these challenges is essential to facilitate the translation of nanocarrier-based therapies from research to clinical practice [93].

The clinical translation of nanocarrier-based systems for diabetes management is still in its early stages, although significant progress has been made in recent years. Several nanoformulations, particularly for insulin delivery, have advanced to preclinical and early-phase clinical trials, demonstrating improved pharmacokinetics, enhanced bioavailability, and better patient compliance compared to conventional therapies [94]. Oral insulin formulations utilizing nanoparticles and lipid-based carriers are among the most actively investigated approaches. Similarly, glucose-responsive and stimuli-sensitive systems are being explored for their potential to provide automated and precise glycemic control. However, only a limited number of nanocarrier-based antidiabetic formulations have reached advanced clinical trial phases or regulatory approval, largely due to safety concerns, manufacturing challenges, and regulatory complexities. Continued research, long-term clinical studies, and improved understanding of nanocarrier behavior in humans are necessary to accelerate their clinical adoption and establish their role in routine diabetes management [95].

9. Future Perspectives

Smart nanomedicine represents the next generation of nanocarrier-based drug delivery systems, integrating sensing, targeting, and controlled release functionalities into a single platform. In diabetes management, smart nanocarriers are being designed to respond dynamically to physiological cues such as blood glucose levels, pH variations, or enzymatic activity, thereby enabling real-time, self-regulated drug delivery [96]. These systems aim to closely mimic the natural function of pancreatic β-cells by releasing insulin only when required, reducing the risk of hypoglycemia and improving overall glycemic control. Advances in materials science, such as the development of multifunctional polymers and hybrid nanostructures, are further enhancing the capabilities of these systems. Additionally, integration with wearable devices and biosensors may allow continuous monitoring and automated drug release, paving the way for closed-loop therapeutic systems. Although still largely in the experimental stage, smart nanomedicine holds immense potential to revolutionize diabetes treatment by offering more precise, efficient, and patient-friendly solutions [97].

Personalized therapy is emerging as a key paradigm in modern healthcare, focusing on tailoring treatment strategies to individual patient characteristics, including genetic profile, disease progression, lifestyle, and metabolic response. Nanocarrier-based drug delivery systems can play a significant role in enabling personalized diabetes management by allowing customization of drug type, dose, and release profile [98]. For instance, nanocarriers can be engineered to deliver drugs at specific rates or target particular tissues based on patient-specific needs. Advances in genomics, proteomics, and metabolomics are providing deeper insights into the heterogeneity of diabetes, enabling the development of individualized treatment approaches. Furthermore, patient-specific factors such as age, comorbidities, and drug tolerance can be incorporated into nanocarrier design to optimize therapeutic outcomes. Personalized nanomedicine has the potential to improve treatment efficacy, minimize adverse effects, and enhance patient adherence, ultimately leading to better long-term disease management [99].

The integration of artificial intelligence (AI) with nanocarrier-based drug delivery systems is opening new avenues for innovation in diabetes therapy. AI and machine learning algorithms can be utilized to optimize nanocarrier design by predicting drug–carrier interactions, stability, release kinetics, and targeting efficiency. These computational tools can significantly accelerate the development process by reducing reliance on trial-and-error experimentation. In addition, AI-driven data analysis can help in identifying patterns in patient responses, enabling more accurate prediction of therapeutic outcomes and facilitating personalized treatment strategies. AI can also be integrated with smart nanocarriers and biosensors to develop intelligent drug delivery systems capable of real-time decision-making, such as adjusting insulin release based on continuous glucose monitoring data. This convergence of nanotechnology and digital health has the potential to create highly efficient, adaptive, and autonomous therapeutic systems for diabetes management [100].

Despite significant advancements in nanocarrier-based drug delivery systems, their successful clinical translation remains a major challenge. Bridging the gap between laboratory research and clinical application requires overcoming several barriers, including large-scale manufacturing, reproducibility, regulatory approval, and long-term safety evaluation. Ensuring batch-to-batch consistency and cost-effective production is essential for commercial viability [101]. Additionally, extensive preclinical and clinical studies are needed to establish the safety, efficacy, and pharmacokinetic profiles of nanocarrier systems in humans. Regulatory frameworks for nanomedicines are still evolving, and clear guidelines are required to streamline the approval process. Collaboration between researchers, clinicians, industry stakeholders, and regulatory authorities is crucial to address these challenges. With continued advancements and interdisciplinary efforts, nanocarrier-based therapies have the potential to transition from experimental concepts to clinically approved solutions, significantly improving the management of diabetes mellitus in the future [102].

10. Conclusion

Nanocarrier-based drug delivery systems represent a significant advancement in the management of diabetes mellitus by effectively addressing the limitations of conventional therapeutic approaches. Traditional treatments, including insulin injections and oral hypoglycemic agents, are often associated with challenges such as poor bioavailability, frequent dosing, systemic side effects, and low patient compliance. The application of nanotechnology has enabled the development of innovative delivery platforms capable of enhancing drug stability, improving absorption, and facilitating controlled and targeted release of antidiabetic agents. Various nanocarrier systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, and nanoemulsions, have demonstrated considerable potential in improving therapeutic outcomes. These systems not only protect sensitive biomolecules like insulin from degradation but also allow for alternative, non-invasive routes of administration such as oral, nasal, and transdermal delivery. Moreover, the emergence of smart and stimuli-responsive nanocarriers, particularly glucose-responsive systems, offers a promising approach toward achieving self-regulated and physiologically relevant drug delivery. Despite these advancements, several challenges remain, including concerns related to safety, toxicity, scalability, and regulatory approval. The transition of nanocarrier-based systems from laboratory research to clinical practice requires extensive preclinical and clinical evaluation, along with standardized regulatory frameworks. Nanocarrier-based drug delivery systems hold immense potential to revolutionize diabetes management by improving therapeutic efficacy, enhancing patient compliance, and enabling personalized treatment strategies. Continued research, technological innovation, and interdisciplinary collaboration will be essential to fully realize their clinical potential and establish them as a cornerstone in the future treatment of diabetes mellitus.

Reference

[1] E. M. Brouwer-Brolsma *et al.*, “Nutrition Questionnaires plus (NQplus) study, a prospective study on dietary determinants and cardiometabolic health in Dutch adults,” *BMJ Open*, 2018, doi: 10.1136/bmjopen-2017-020228.

[2] K. Au and A. Chau, “Obstetric Anesthesia for Co-morbid Conditions,” *Anesth. Analg.*, 2019, doi: 10.1213/ane.0000000000004262.

[3] D. F. Sumah, G. J. Wakanno, V. Y. Lameky, and B. V. Batlajery, “The combination of self acupressure Taixi KD-3 and Zusanli ST-36 Effectively controls blood glucose for type 2 diabetics,” *Multidiscip. Sci. J.*, 2025, doi: 10.31893/multiscience.2025473.

[4] M. Kaniawati, S. S. Muthmainah, and L. Herliana, “Implementation of Hadith in Contemporary Islamic Law: A Case Study of The Determination of Fatwa Law in the Exchange of New Money Ahead of Eid in Indonesia,” *J. Impresi Indones.*, 2025, doi: 10.58344/jii.v4i5.6523.

[5] A. Jain and S. Dawre, “A Comprehensive Review on Prospects of Polymeric Nanoparticles for Treatment of Diabetes Mellitus: Receptors-Ligands, In vitro & In vivo Studies,” *Recent Pat. Nanotechnol.*, 2023, doi: 10.2174/1872210517666230803091245.

[6] C. J.M. *et al.*, “Cost-effectiveness of intervention combinations towards the elimination of vertical transmission of HIV in limited-resource settings: a mathematical modelling study,” *Lancet Glob. Heal.*, 2024.

[7] S. Balasubramaniyam, T. Rathinam, M. Srinivasan, and S. Jayarani, “Nanocarrier-based insulin delivery: A leap towards a needle-free future,” 2025. doi: 10.1016/j.ntm.2025.100093.

[8] F. Islam *et al.*, “Corrigendum to ‘Multifaceted role of polyphenols in the treatment and management of neurodegenerative diseases’ [Chemosphere 307 (2022) 136020] (Chemosphere (2022) 307(P3), (S0045653522025139), (10.1016/j.chemosphere.2022.136020)),” 2023. doi: 10.1016/j.chemosphere.2023.139655.

[9] M. Monaghan, B. L. Bryant, H. Inverso, H. R. Moore, and R. Streisand, “Young Children with Type 1 Diabetes: Recent Advances in Behavioral Research,” 2022. doi: 10.1007/s11892-022-01465-0.

[10] S. Khan, B. Huda, F. Bhurka, R. Patnaik, and Y. Banerjee, “Molecular and Immunomodulatory Mechanisms of Statins in Inflammation and Cancer Therapeutics with Emphasis on the NF-κB, NLRP3 Inflammasome, and Cytokine Regulatory Axes,” 2025. doi: 10.3390/ijms26178429.

[11] K. I. Aamodt and A. C. Powers, “The pathophysiology, presentation and classification of Type 1 diabetes,” *Diabetes, Obes. Metab.*, 2025, doi: 10.1111/dom.16628.

[12] A. Tegehall, O. Korsgren, S. Ingvast, G. Gasparyan, L. Granlund, and M. Lundberg, “Islet delta-cell architecture is remodelled in the human pancreas during type 1 diabetes,” *Sci. Rep.*, 2025, doi: 10.1038/s41598-025-04471-w.

[13] A. M. Luckett, M. N. Weedon, G. Hawkes, R. D. Leslie, R. A. Oram, and S. F. A. Grant, “Utility of genetic risk scores in type 1 diabetes,” 2023. doi: 10.1007/s00125-023-05955-y.

[14] R. Gesuita *et al.*, “Frequency and clinical characteristics of children and young people

with type 2 diabetes at diagnosis from five world regions between 2012 and 2021: data from the SWEET Registry," *Diabetologia*, 2025, doi: 10.1007/s00125-024-06283-5.

[15] M. Apostolopoulou, V. Lambadiari, M. Roden, and G. D. Dimitriadis, "Insulin Resistance in Type 1 Diabetes: Pathophysiological, Clinical, and Therapeutic Relevance," 2025. doi: 10.1210/endrev/bnae032.

[16] M. Hendrianingtyas and S. A. Pradati, "Visceral Adiposity Index and Insulin Resistance in Diabetes Mellitus Type 2," *J. Biomed. Transl. Res.*, 2024, doi: 10.14710/jbtr.v10i3.23505.

[17] Y. Miyachi, T. Miyazawa, and Y. Ogawa, "HNF1A Mutations and Beta Cell Dysfunction in Diabetes," *Int. J. Mol. Sci.*, 2022, doi: 10.3390/ijms23063222.

[18] D. Yao, Y. GangYi, and W. QiNan, "Autophagic dysfunction of β cell dysfunction in type 2 diabetes, a double-edged sword," 2021. doi: 10.1016/j.gendis.2020.03.003.

[19] H. Amsalu, M. Hailu, A. Asefa, M. Ayenew, and T. Yosef, "The effect of lifestyle factors on chronic complications of diabetes at public health hospitals in Southwest Ethiopia," *Sci. Rep.*, 2024, doi: 10.1038/s41598-024-69527-9.

[20] S. Selim, "Frequency and pattern of chronic complications of diabetes and their association with glycemic control among adults with type 2 diabetes in Bangladesh," *Diabetes Metab. Syndr. Clin. Res. Rev.*, 2017, doi: 10.1016/j.dsx.2017.03.010.

[21] R. Sharma *et al.*, "Emerging trends in nano-based antidiabetic therapeutics: a path to effective diabetes management," 2023. doi: 10.1039/d3ma00159h.

[22] N. Thembane, S. Hlatshwayo, M. Ngcobo, P. Ngubane, and N. Gqaleni, "Review on the Anti-Hyperglycemic Potential of Psidium guajava and Seriphium plumosum L.," 2024. doi: 10.3390/plants13121608.

[23] D. M. Trasca *et al.*, "The Antidiabetic Activity of Wild-Growing and Cultivated Medicinal Plants Used in Romania for Diabetes Mellitus Management: A Phytochemical and Pharmacological Review," 2025. doi: 10.3390/ph18071035.

[24] P. Kapoor *et al.*, "Flaxseed in Diabetes Management: Nutritional and Therapeutic Insights," 2025. doi: 10.1007/s13668-025-00696-3.

[25] N. K. F. M. Jayaningsih, N. W. Nuratningsih, and N. K. T. Wirawati, "Porang (Amorphophallus muelleri Blume) and its potential in diabetes management," *Pharm. Reports*, 2025, doi: 10.51511/pr.90.

[26] M. Banerjee *et al.*, "A Systematic Review on Synthetic Drugs and Phytopharmaceuticals Used to Manage Diabetes," *Curr. Diabetes Rev.*, 2019, doi: 10.2174/1573399815666190822165141.

[27] Z. Akram, "Insulin therapy: Associated challenges in Type 2 Diabetes," *Sci. Prog. Res.*, 2022, doi: 10.52152/spr/2022.160.

[28] M. Li, D. Law, S. Zhu, A. A. kareem Najm, S. Fazry, and B. A. Othman, "Extraction, purification, characterization and antidiabetic mechanisms of plant polysaccharides: a critical review," 2024. doi: 10.1515/tjb-2024-0071.

[29] S. K. Pattanaik, P. M. Anil, S. Jena, and D. Rath, "Interlinking diabetes and Alzheimer's disease: A pathway through medicinal plant-based treatments," 2025. doi: 10.1016/j.jep.2025.120092.

[30] A. Parfianowicz and Alicja Surma, "GLP-1 and SGLT2 Therapies in Type 2 Diabetes Mellitus. Cutting-Edge Approaches to Advancing Diabetes Care," *J. Educ. Heal.*

Sport, 2025, doi: 10.12775/jehs.2025.78.57478.

[31] N. Ebrahimi, A. Ranjbar, S. Shahabi, and S. Afrasiabi, “Nanocarrier-based Drug Delivery Systems to Enhance Antimicrobial Photodynamic Therapy in Dental Applications: A Review,” 2025. doi: 10.1208/s12249-025-03155-y.

[32] M. Sohail *et al.*, “Nanocarrier-based Drug Delivery System for Cancer Therapeutics: A Review of the Last Decade,” *Curr. Med. Chem.*, 2020, doi: 10.2174/0929867327666201005111722.

[33] T. Yousaf, I. Ahmad, Z. Younas, M. H. Hamdard, and Z. ur R. Mashwani, “Emerging Plant-Based Nanotechnological Advances and Molecular Insights for Type-2 Diabetes, Diagnosis and Treatments-Recent Trends and Future Prospects,” 2025. doi: 10.1021/acsomega.5c01900.

[34] A. Bhardwaj, S. Verma, A. Agnihotri, and H. R. Chitme, “Emerging nanotechnology-based therapies in the treatment of diabetes: recent developments and future opinion,” 2025. doi: 10.1080/03639045.2025.2548844.

[35] K. K Karunakar, B. V. Cheriyan, K. R, G. M, and A. B, “‘Therapeutic advancements in nanomedicine: The multifaceted roles of silver nanoparticles,’” 2024. doi: 10.1016/j.biotno.2024.05.002.

[36] Z. Qi, Z. Yan, G. Tan, S. C. Kundu, and S. Lu, “Smart Responsive Microneedles for Controlled Drug Delivery,” 2023. doi: 10.3390/molecules28217411.

[37] W. A. Gómez *et al.*, “Leptin Signaling and Its Relationship with Obesity-induced Insulin Resistance: A Bioinformatics-assisted Review,” 2025. doi: 10.14218/GE.2024.00039.

[38] A. Zielinska *et al.*, “Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology,” 2020. doi: 10.3390/molecules25163731.

[39] M. F. S. Orozco *et al.*, “Antimicrobial Polymeric Nanoparticles in Endodontics: A Systematic Review,” 2025. doi: 10.1155/jnt/3896901.

[40] B. Frierson *et al.*, “Production and Characterization of Double-membrane Echogenic Liposomal Carrier-loaded Alteplase for Thrombolytic Treatment of Empyema,” *Am. J. Respir. Crit. Care Med.*, 2025, doi: 10.1164/ajrccm.2025.211.abstracts.a4507.

[41] X. Liu *et al.*, “Curcumin and its novel formulations for diabetes mellitus and its complications: a review,” 2025. doi: 10.1039/d5fo00988j.

[42] S. Dhyani, M. Butola, V. Sautha, and V. Jakhmola, “RECENT ADVANCES IN TREATMENT APPROACHES FOR DIABETES MELLITUS AND RELATED COMPLICATIONS: A REVIEW,” 2025. doi: 10.22159/ijap.2025v17i2.53184.

[43] K. A., K. M., and K. S., “Drug Delivery in Rare Diseases: Orphan Drugs and Therapies,” *Methods Pharmacol. Toxicol.*, 2025.

[44] M. Qushawy *et al.*, “Optimized Nanostructured Lipid Carriers for Metformin: Enhanced Anti-Inflammatory Activity and Protection Against Type 2 Diabetes-Induced Organ Damage,” *Int. J. Nanomedicine*, 2025, doi: 10.2147/IJN.S506631.

[45] F. Stojceski, G. Grasso, L. Pallante, and A. Danani, “Molecular and Coarse-Grained Modeling to Characterize and Optimize Dendrimer-Based Nanocarriers for Short Interfering RNA Delivery,” *ACS Omega*, 2020, doi: 10.1021/acsomega.9b03908.

[46] S. Y. Park *et al.*, “Effects of charge distribution and degree of methylesterification of pectin emulsifier on bioaccessibility of curcumin incorporated in nanoemulsions,” *Int.*

J. Biol. Macromol., 2024, doi: 10.1016/j.ijbiomac.2024.135189.

[47] Y. Wang, H. Li, A. Rasool, H. Wang, R. Manzoor, and G. Zhang, "Polymeric nanoparticles (PNPs) for oral delivery of insulin," 2024. doi: 10.1186/s12951-023-02253-y.

[48] C. Roy, A. Gandhi, S. Manna, and S. Jana, "Fabrication and evaluation of carboxymethyl guar gum-chitosan interpenetrating polymer network (IPN) nanoparticles for controlled drug delivery," *Med. Nov. Technol. Devices*, 2024, doi: 10.1016/j.medntd.2024.100300.

[49] H. Wu, J. Nan, L. Yang, H. J. Park, and J. Li, "Insulin-loaded liposomes packaged in alginate hydrogels promote the oral bioavailability of insulin," *J. Control. Release*, 2023, doi: 10.1016/j.jconrel.2022.11.032.

[50] L. Herbster *et al.*, "Liposomes Containing Tetraether Lipids and Cell-Penetrating Peptides as Platform Technology for Oral Delivery of Peptides: A Comparative Study on GLP-1 Analogs," *Nano Sel.*, 2025, doi: 10.1002/nano.70010.

[51] I. Raghunath, M. Koland, C. Sarathchandran, S. Saoji, and N. Rarokar, "Design and optimization of chitosan-coated solid lipid nanoparticles containing insulin for improved intestinal permeability using piperine," *Int. J. Biol. Macromol.*, 2024, doi: 10.1016/j.ijbiomac.2024.135849.

[52] N. A. Yusuf, R. Aksa, F. Juniawan, C. Sekolah, T. Ilmu, and F. Makassar, "Optimasi Variasi Konsentrasi Lipid Terhadap Karakteristik Fisik Solid Lipid Nanoparticle (SLN) Glibenklamid," *J. Ilm. Manuntung*, 2020.

[53] I. Welengodage and N. P. Katuwavila, "Recent advancements in lipid nanoparticle technology for oral insulin delivery," *Univ. Colombo Rev.*, 2024, doi: 10.4038/ucr.v5i1.134.

[54] S. Faiz *et al.*, "Pioglitazone-loaded nanostructured lipid carriers: In-vitro and in-vivo evaluation for improved bioavailability," *J. Drug Deliv. Sci. Technol.*, 2023, doi: 10.1016/j.jddst.2022.104041.

[55] A. Hosseini Sharifabad, T. Behzad, and M. Salami-Kalajahi, "Smart glucose-responsive PAMAM dendrimers anchored on nanocrystalline cellulose for controlled insulin release," *Int. J. Biol. Macromol.*, 2025, doi: 10.1016/j.ijbiomac.2025.145235.

[56] D. E. Uti *et al.*, "Combined Hyaluronic Acid Nanobioconjugates Impair CD44-Signaling for Effective Treatment Against Obesity: A Review of Comparison with Other Actors," 2025. doi: 10.2147/IJN.S529250.

[57] A. K. P. Lorenzett, V. A. de Lima, C. O. P. da Fonseca, and R. M. Mainardes, "Nanoemulsions and Microemulsions for Intranasal Drug Delivery: A Bibliometric Analysis and Emerging Trends (2004–2024)," *Pharmaceutics*, 2025, doi: 10.3390/pharmaceutics17091104.

[58] A. R. Koli *et al.*, "Microemulsions : A Potential Novel Drug Delivery System Acta Scientifica International Journal of Pharmaceutical Science Microemulsions : A Potential Novel Drug Delivery System," *Int. J. Pharm. Pharm. Sci.*, 2021.

[59] S. Albetawi, A. Abdalhafez, A. Abu-Zaid, A. Matrouk, and N. Alhourani, "Recent solubility and dissolution enhancement techniques for repaglinide a BCS class II drug: a review," *Pharmacia*, 2021, doi: 10.3897/PHARMACIA.68.E66586.

[60] F. Chovancová *et al.*, "Synthesis of nickel dopped chitosan nanoparticles as a novel platform for electrochemical insulin detection," *Biosens. Bioelectron. X*, 2025, doi:

10.1016/j.biosx.2025.100624.

[61] C. Taverna *et al.*, “Probing the effect of the molecular interface of gold nanoparticles on the disassembly of insulin amyloid fibrils,” *Int. J. Biol. Macromol.*, 2025, doi: 10.1016/j.ijbiomac.2025.141735.

[62] A. Subramanian, “Current Strategies and Challenges in Stimuli-Responsive Nanocarriers for Insulin Delivery,” 2025. doi: 10.1002/slct.202500538.

[63] S. Sarkhel *et al.*, “Nanotechnology-Based Approaches for the Management of Diabetes Mellitus: An Innovative Solution to Long-Lasting Challenges in Antidiabetic Drug Delivery,” 2024. doi: 10.3390/pharmaceutics16121572.

[64] A. Elsayed, M. Al-Remawi, N. Jaber, and K. M. Abu-Salah, “Advances in buccal and oral delivery of insulin,” 2023. doi: 10.1016/j.ijpharm.2023.122623.

[65] C. Palde, T. Barot, G. S. Chakraborthy, and L. D. Patel, “PEPTIDE DELIVERY VIA NASAL ROUTE: EXPLORING RECENT DEVELOPMENTS AND APPROACHES,” 2024. doi: 10.22159/ijap.2024v16i4.50626.

[66] F. H. Nabila *et al.*, “Ionic liquid-mediated ethosome for transdermal delivery of insulin,” *Chem. Commun.*, 2024, doi: 10.1039/d3cc06130b.

[67] Z. Jan *et al.*, “Micro and nanoneedles for transdermal delivery of insulin,” 2025. doi: 10.1016/j.jddst.2025.107128.

[68] R. Naqvi, Z. Ahmed, and S. Zameer, “Recombinant Nanobiotechnology for Swallowable Insulin: Innovations in Noninvasive Diabetes Therapy,” *Ricos Biol.*, 2025, doi: 10.33687/ricosbiol.03.011.90.

[69] M. Hussain, A. Hafeez, and S. P. Kushwaha, “Nanoformulation mediated transdermal delivery of anti-diabetic drugs: an updated review,” 2023. doi: 10.1016/j.ipha.2023.08.009.

[70] J. Ren *et al.*, “Combined Oxaliplatin with 5-Fluorouracil for Effective Chemotherapy Against Gastric Cancer in Animal Model,” *Int. J. Nanomedicine*, 2025, doi: 10.2147/IJN.S520603.

[71] B. Sharmah *et al.*, “Glucose-Responsive Insulin Delivery via Surface-Functionalized Titanium Dioxide Nanoparticles: A Promising Theragnostic against Diabetes Mellitus,” *ACS Appl. Bio Mater.*, 2025, doi: 10.1021/acsabm.4c01426.

[72] S. F. T. Pinto, H. A. Santos, and B. F. C. C. Sarmento, “New insights into nanomedicines for oral delivery of glucagon-like peptide-1 analogs,” 2024. doi: 10.1002/wnan.1952.

[73] E. Budiawan, Y. L. Gloria, and A. Wulandari, “POLA PENGGUNAAN OBAT ANTIDIABETES PADA PASIEN RAWAT INAP RSUD ANUTAPURA PALU,” *JIFI (Jurnal Ilm. Farm. Imelda)*, 2023, doi: 10.52943/jifarmasi.v7i1.1484.

[74] V. Mohan *et al.*, “Optimizing Type 2 Diabetes Management: The Efficacy and Safety of Gliclazide in Clinical Practice,” 2025. doi: 10.4103/jod.jod_50_25.

[75] S. Biswas and S. Rudra, “Development of various drug delivery system for semaglutide: a wonder drug for diabetes,” *Adamas Tech. Rev.*, 2025, doi: 10.65024/atr.v2i2.09.

[76] P. Bidulka *et al.*, “Comparative effectiveness of second line oral antidiabetic treatments among people with type 2 diabetes mellitus: emulation of a target trial using routinely collected health data,” *BMJ*, 2024, doi: 10.1136/bmj-2023-077097.

[77] J. R. Nandikola *et al.*, “Antidiabetic Management Strategies for Treatment of Polycystic Ovarian Syndrome,” *J. Neonatal Surg.*, 2025, doi: 10.52783/jns.v14.1517.

[78] N. J.C.G.L. *et al.*, “Analysis of the effectiveness of cinnamon (Cinnamomum verum) in the reduction of glycemic and lipidic levels of adults with type 2 diabetes: A study protocol,” *Med. (United States)*, 2020.

[79] W. Zhu *et al.*, “Analysis of patents issued in China for antihyperglycemic therapies for type 2 diabetes mellitus,” *Front. Pharmacol.*, 2019, doi: 10.3389/fphar.2019.00586.

[80] M. Abbasi, D. A. Boka, and H. DeLoit, “Nanomaterial-Enhanced Microneedles: Emerging Therapies for Diabetes and Obesity,” 2024. doi: 10.3390/pharmaceutics16101344.

[81] K. Asogwa, T. Awojulu, N. Asogwa, S. Ameh, and J. Ezeani, “Sugar-Smart Nano Boosters: Mesoporous Silica Nanoparticles for Dual-Action Therapy in Obesity-Linked Diabetes,” *Int. J. Futur. Eng. Innov.*, 2025, doi: 10.54660/ijfei.2025.2.4.07-16.

[82] D. Mojeeb, M. Thakur, R. S. Khan, P. Chandel, and A. Sharma, “International Journal of Multidisciplinary Research in Biotechnology , Role of Pharmacogenomics in Personalized Medicine : A New Frontier in Drug Therapy Optimization,” no. 1, pp. 50–63, 2025.

[83] A. Bandyopadhyay *et al.*, “Ligand-based active targeting strategies for cancer theranostics,” 2023. doi: 10.1007/s00210-023-02612-4.

[84] S. Ahmad, M. Gojar, A. Sharma, M. Thakur, and P. Chandel, “International Journal of Multidisciplinary Research in Biotechnology , Retinal Organoids in Precision Ophthalmology : Advances , Applications , and Translational Challenges,” pp. 9–26, 2025.

[85] S. K. Kushwaha, P. Chandel, T. Singh, M. Thakur, and U. Pradesh, “Formulation and Evaluation of a Multicomponent Herbal Shampoo for Enhanced Hair and Scalp Health Department of Pharmacy , IIMT College of Medical Sciences , IIMT University , Ganga Nagar , Meerut- School of Pharmacy , Deshbhagat University Amloh Road , Ma,” pp. 373–383.

[86] M. Pourmadadi *et al.*, “Development and evaluation of SA/PVP/γ-Al_2O_3 nanocarriers for targeted delivery of curcumin in colon cancer therapy,” *J. Drug Deliv. Sci. Technol.*, 2025, doi: 10.1016/j.jddst.2025.106632.

[87] Z. Ali, P. Chandel, A. Sharma, M. Thakur, and F. Akhter, “International Journal of Multidisciplinary Research in Biotechnology , Natural Products and Phytochemicals in Modern Drug Discovery : Mechanistic Insights , Barriers , and Future Opportunities,” no. October, pp. 20–35, 2025.

[88] F. Akhter, P. Chandel, A. Sharma, M. Thakur, S. Alam, and Z. Ali, “International Journal of Multidisciplinary Research in Biotechnology , Smart Nanotechnology-Based Drug Delivery Systems : Recent Advances and Future Prospects in Stimuli-Responsive Targeted Therapy,” no. October, pp. 1–19, 2025.

[89] P. Chandel, T. Singh, A. Sharma, F. Sahib, and M. Gobindgarh, “Emerging Biomarkers for Early Detection of Alzheimer ’ s Disease : Progress and Challenges School of Pharmacy , Deshbhagat University , off to NH-44 , Amloh Road , Mandi Gobindgarh District,” pp. 364–372.

[90] Manisha Dev and Pallavi Chandel, “Nanostructured Lipid Carriers in Pulmonary Drug Delivery: Progress and Prospects,” *Curr. Pharm. Res.*, pp. 131–143, 2025, doi:

10.63785/cpr.2025.1.1.131143.

[91] M. H. Karami *et al.*, “Novel chitosan/γ-alumina/carbon quantum dot hydrogel nanocarrier for targeted drug delivery,” *Int. J. Biol. Macromol.*, 2023, doi: 10.1016/j.ijbiomac.2023.126280.

[92] P. Uhl *et al.*, “A Nanocarrier Approach for Oral Peptide Delivery: Evaluation of Cell-Penetrating-Peptide-Modified Liposomal Formulations in Dogs,” *Adv. Ther.*, 2023, doi: 10.1002/adtp.202300021.

[93] S. Kumar, S. Kaul, N. Jain, C. Jain, and M. Pandey, “Gouty Arthritis Treatment: Advancements in Topical Lipid-Based Nanocarrier Delivery Systems,” 2025. doi: 10.34172/apb.44012.

[94] K. Wang, R. Yang, J. Li, H. Wang, L. Wan, and J. He, “Nanocarrier-based targeted drug delivery for Alzheimer’s disease: addressing neuroinflammation and enhancing clinical translation,” 2025. doi: 10.3389/fphar.2025.1591438.

[95] D. Sridhar, R. Manikandan, Y. Dhanapal, S. Khute, and P. Subash, “Artificial intelligence in predicting personalized nanocarrier formulations for herbal drugs: Bridging phytomedicine and precision nanotechnology,” 2025. doi: 10.1016/j.ipha.2025.08.001.

[96] R. Biswas *et al.*, “Chitosan and Its Derivatives as Nanocarriers for Drug Delivery,” 2025. doi: 10.3390/molecules30061297.

[97] S. S. Deshmukh, H. P. Nijhawan, and K. S. Yadav, “Chitosan-based copolymeric nanocarrier systems: A novel paradigm for targeted breast cancer therapy,” *Int. J. Biol. Macromol.*, 2025, doi: 10.1016/j.ijbiomac.2025.145537.

[98] L. Mastrodomenico *et al.*, “Personalized Systemic Therapies in Hereditary Cancer Syndromes,” 2023. doi: 10.3390/genes14030684.

[99] H. Guo *et al.*, “The Pivotal Role of Preclinical Animal Models in Anti-Cancer Drug Discovery and Personalized Cancer Therapy Strategies,” 2024. doi: 10.3390/ph17081048.

[100] C. Xu *et al.*, “Etiological Diagnosis and Personalized Therapy for Hypertension: A Hypothesis of the REASOH Classification,” 2023. doi: 10.3390/jpm13020261.

[101] A. Sami, A. Javed, D. U. Ozsahin, I. Ozsahin, K. Muhammad, and Y. Waheed, “Genetics of diabetes and its complications: a comprehensive review,” 2025. doi: 10.1186/S13098-025-01748-Y.

[102] I. I. Dedov *et al.*, “EPIDEMIOLOGY AND KEY CLINICAL AND THERAPEUTIC INDICATORS OF DIABETES MELLITUS IN RUSSIAN FEDERATION ACCORDING TO THE WORLD HEALTH ORGANIZATION’S STRATEGY GOALS,” *Diabetes Mellit.*, 2025, doi: 10.14341/DM13292.