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Smart Nanocarriers for Targeted Delivery of Antidiabetic Agents in Obesity-Linked Diabetes

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ABSTRACT

Obesity-linked diabetes, driven by chronic inflammation, ectopic lipid deposition, and multi-organ insulin resistance, remains difficult to treat with conventional pharmacotherapy due to poor drug solubility, rapid degradation, off-target effects, and suboptimal exposure in key metabolic tissues. Smart nanocarriers engineered at the 1–200 nm scale with programmable composition, surface chemistry, and stimuli-responsiveness offer a way to concentrate antidiabetic payloads in adipose tissue, liver, skeletal muscle, pancreatic islets, and the gut while minimizing systemic toxicity. This review surveys design principles and translational considerations for polymeric, lipidic, inorganic, and biomimetic nanocarriers that deliver small molecules, peptides/proteins (e.g., insulin, GLP-1 agonists), and nucleic acids (siRNA/ASO/mRNA/CRISPR). We highlight active homing strategies (e.g., hepatocyte ASGPR–GalNAc, adipose-vasculature–targeting peptides, β-cell GLP-1R ligands, macrophage mannose/CD206), and "smart" release modalities triggered by glucose, pH, redox/ROS, enzymes, heat, ultrasound, or magnetic fields. We critically examine oral, transdermal microneedle, and subcutaneous depot routes and discuss pharmacokinetics, immunogenicity, scale-up, and regulatory quality attributes. Finally, we outline frontier opportunities for organelle-level targeting, multi-omic personalization, and combined metabolic–immune modulation together with practical roadblocks such as manufacturing reproducibility, in vivo heterogeneity of human adipose depots, and equitable access. Collectively, smart nanocarriers are poised to upgrade the therapeutic index of antidiabetic regimens in obesity, provided that material safety, targeting specificity, and manufacturability are addressed in human-centric studies.

Keywords: targeted drug delivery; nanomedicine; obesity; type 2 diabetes; stimuli-responsive nanoparticles; GLP-1; insulin; GalNAc; adipose targeting; microneedles

INTRODUCTION

Obesity-linked diabetes, primarily type 2 diabetes mellitus (T2DM), has emerged as one of the most pressing global health challenges of the 21st century[1]. The condition represents the culmination of intricate metabolic, inflammatory, and endocrine derangements that progressively erode glucose homeostasis.[2, 3] Unlike type 1 diabetes, where autoimmune destruction of pancreatic β-cells dominates the pathophysiology, obesity-linked diabetes originates in the dysfunctional expansion of adipose tissue[4]. Hypertrophied adipocytes, hypoxic stress, and inflammatory remodeling of fat depots generate a state of chronic low-grade inflammation, releasing pro-inflammatory cytokines such as TNF-α and IL-6 into circulation[5]. These factors amplify insulin resistance across metabolic tissues, including the liver, skeletal muscle, and adipose tissue itself, creating a vicious cycle of metabolic inflexibility. In parallel, mitochondrial stress and altered adipokine secretion (e.g., leptin resistance, decreased adiponectin) further destabilize systemic insulin sensitivity and nutrient utilization[6].

Clinically, therapeutic management of obesity-linked diabetes relies on pharmacological interventions that improve glycemia and reduce long-term complications. Standard agents include metformin, which reduces hepatic glucose production; thiazolidinediones, which enhance peripheral insulin sensitivity via PPARγ activation; and more recent classes such as SGLT2 inhibitors, DPP-4 inhibitors, and incretin-based therapies (GLP-1 receptor agonists)[7]. Despite demonstrated efficacy, these agents are limited by significant drawbacks. Metformin often causes gastrointestinal intolerance, while thiazolidinediones can induce fluid retention and increase cardiovascular risks. Peptide-based therapies such as GLP-1 analogs are effective but limited by poor oral bioavailability, requiring injections, and they do not achieve adequate exposure in all relevant tissues[8, 9]. Furthermore, many of these agents do not address the full spectrum of metabolic dysfunctions particularly the inflammatory, mitochondrial, and gut microbiome-related dimensions of obesity-linked diabetes.

To overcome these challenges, nanotechnology-based drug delivery systems are being actively investigated. Nanocarriers engineered nanoscale platforms capable of encapsulating and delivering therapeutic cargo hold several advantages over conventional formulations[10]. By leveraging principles of controlled biodistribution, surface functionalization, and stimuli-responsive release, nanocarriers can increase local drug concentrations at sites of metabolic dysfunction, thereby enhancing therapeutic efficacy. Importantly, they can reduce off-target exposure, minimizing systemic toxicity, and enable the delivery of agents previously considered "undeliverable," such as peptides, biologics, or nucleic acids[11]. Moreover, smart nanocarriers can incorporate closed-loop control systems, releasing drugs only in response to specific stimuli (e.g., pH, reactive oxygen species, enzymatic activity), which aligns drug delivery with the dynamic pathophysiological states of the disease[12]. This review highlights the potential of smart nanocarriers as next-generation therapeutics in the management of obesity-linked diabetes. Specifically, it focuses on strategies for tissue- and cell-specific targeting, as well as on-demand release mechanisms tailored to metabolic dysfunction. By integrating advances in nanomaterials science with a deep understanding of metabolic disease biology, these systems offer the promise of reshaping the therapeutic landscape. The ultimate goal is not only to achieve superior glycemic control but also to address the broader multi-organ dysfunction that underpins obesity-linked diabetes, thereby transforming disease management into a more precise, patient-tailored endeavor.

2. Pathophysiological Targets in Obesity-Linked Diabetes

Obesity-linked diabetes is characterized by the convergence of multiple pathological processes across diverse organ systems. Effective therapeutic strategies must therefore account for the multi-organ interplay that drives disease progression. Adipose tissue, liver, skeletal muscle, pancreatic islets, and the gut–microbiome axis represent the principal targets whose dysfunction culminates in impaired glucose metabolism and insulin resistance. In adipose tissue, the transition from healthy expansion to maladaptive hypertrophy marks the first step toward metabolic disease[13]. Enlarged adipocytes develop hypoxia and fibrosis, creating an inflammatory microenvironment dominated by M1-like macrophages. These macrophages, alongside stressed adipocytes, secrete TNF-α, IL-6, and free fatty acids, which enter circulation and impair insulin receptor signaling in peripheral tissues[14, 15]. Visceral adipose depots are particularly detrimental, as their direct drainage into the portal vein exposes the liver to concentrated inflammatory and lipolytic products, accelerating hepatic insulin resistance.

The liver plays a central role in glucose regulation, and in obesity-linked diabetes, it becomes a site of profound metabolic disruption. Hepatic steatosis results from an imbalance between lipid uptake and disposal, leading to lipotoxic stress and mitochondrial dysfunction. Activation of stress kinases such as JNK and IKKβ suppresses insulin receptor signaling, causing inappropriate gluconeogenesis and fasting hyperglycemia[16]. This hepatic insulin resistance is a major contributor to elevated fasting plasma glucose levels observed in diabetes. Skeletal muscle, the largest glucose disposal organ in the body, suffers from reduced insulin-stimulated GLUT4 translocation and impaired mitochondrial flexibility. These defects limit the muscle's ability to clear glucose from the circulation after meals, contributing to postprandial hyperglycemia. Additionally, diminished oxidative capacity in muscle cells exacerbates lipid accumulation and metabolic inflexibility[17].

Pancreatic β-cells, initially compensatory in the face of insulin resistance, eventually succumb to chronic metabolic stress. Persistent hyperglycemia, lipotoxicity, and inflammatory signals promote β-cell dedifferentiation[18], apoptosis, and impaired insulin secretion. This decline in β-cell function transforms insulin resistance into overt diabetes, cementing disease progression. The gut and its resident microbiome further influence systemic metabolism. Obesity-induced gut barrier dysfunction increases circulating endotoxins (e.g., LPS), fueling systemic inflammation[18]. Dysbiosis alters bile acid signaling, short-chain fatty acid (SCFA) production, and incretin secretion (GLP-1 and GIP), disrupting glucose and lipid homeostasis. These gut-derived signals represent both a source of pathology and an opportunity for therapeutic modulation[19].

Given the distributed nature of these pathological processes, therapeutic delivery systems must be designed for multi-organ targeting. Moreover, disease states are dynamic, fluctuating with feeding, fasting, and circadian rhythms. An ideal therapeutic system would therefore be capable of responding to these metabolic cues-delivering agents selectively to inflamed adipose depots, steatotic livers, insulin-resistant muscle, or stressed β-cells as needed[20]. This underscores the importance of smart, stimuli-responsive nanocarriers that can adapt delivery in a state-dependent manner, matching pharmacology with the evolving metabolic landscape.

3. Why Nanocarriers? Key Design Principles

Nanocarriers offer a unique opportunity to improve therapeutic outcomes in obesity-linked diabetes by overcoming barriers inherent to conventional pharmacology. Their design requires careful consideration of physicochemical, biological, and manufacturing principles, each of which influences performance, safety, and clinical translation [21]. The size and shape of nanocarriers strongly dictate their biodistribution and pharmacokinetics. Particles between 20-150 nm strike a balance between evading renal clearance and penetrating target tissues. Shape also matters: rod- and disc-shaped particles display improved margination and vascular interactions, while spherical particles are simpler to synthesize and scale. Thus, geometry must be tuned to match therapeutic goals [22]. Surface chemistry governs circulation time and immune interactions. Polyethylene glycol (PEG) has long been used to extend half-life, but repeated administration can elicit anti-

PEG antibodies, compromising efficacy. Alternatives such as zwitterionic polymers or polysaccharides like hyaluronic acid offer stealth properties with lower immunogenic risk. Additionally, surface ligands can confer tissue specificity, such as peptides that bind adipose vasculature or antibodies that recognize β-cell markers [23].

Cargo compatibility is another cornerstone of design. Hydrophobic drugs require encapsulation within lipid bilayers or polymeric matrices, whereas hydrophilic biologics like peptides and proteins are better suited to aqueous cores. Nucleic acids demand cationic or amphiphilic domains to enable condensation and protection. Multi-functional carriers can even co-encapsulate small molecules and biologics for combination therapy [24].

Stability and release properties are determined by the carrier matrix and linkers. Biodegradable polymers like PLGA, polypeptides, and lipid-based systems provide tunable degradation rates. Stimuli-responsive linkers (hydrazone for pH sensitivity, thioketal for ROS sensitivity, or iminoboronate for sugar responsiveness) allow precise control over release kinetics, aligning drug availability with local pathophysiological conditions. Biological interactions pose additional challenges[25]. In vivo, nanocarriers rapidly adsorb a protein corona, which alters biodistribution and cellular uptake. Opsonization and clearance by the mononuclear phagocyte system (MPS) remain significant barriers, often sequestering particles in the liver and spleen. Heterogeneity within disease depots—such as fibrotic versus inflamed adipose tissue—also influences delivery efficiency, necessitating adaptive design [26].

Finally, manufacturability is critical for translation from bench to bedside. Reproducible particle size with low polydispersity (PDI < 0.2) ensures consistent performance. High encapsulation efficiency minimizes waste of costly biologics. Sterility must be maintained through either sterile filtration or terminal sterilization without compromising cargo stability. Long-term stability, both chemical and physical, is necessary for clinical deployment[27]. Taken together, these design principles emphasize that nanocarriers are not merely passive carriers but programmable therapeutic platforms. By fine-tuning their size, surface, cargo, stability, and manufacturability, researchers can engineer delivery systems that address the multifactorial pathophysiology of obesity-linked diabetes [28]. Smart nanocarriers embody the shift from "drug-centered" to "system-centered" pharmacology, where success hinges not only on the molecule but also on how and where it is delivered.

4. Classes of Smart Nanocarriers

4.1 Polymeric Nanoparticles and Micelles

Polymeric nanoparticles and micelles represent one of the most versatile classes of nanocarriers for antidiabetic therapy, largely due to the diversity of polymers available and the tunability of their properties[29, 30]. Commonly used polymers include poly (lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), and amphiphilic PEG-block copolymers, which form micelles that self-assemble in aqueous environments. Natural polymers such as polypeptides, chitosan, and hyaluronan add further biocompatibility and targeting potential[31, 32]. These materials enable precise control over drug release rates, ranging from rapid burst release to extended, multi-day profiles, depending on polymer composition and degradation kinetics. Moreover, they can be engineered with stimuli-responsiveness, making them sensitive to local cues such as enzymatic activity, pH variations, or reactive oxygen species (ROS), which are elevated in inflamed adipose or diabetic liver tissues[25, 33]. Such "smart" carriers ensure that therapeutic molecules are delivered primarily in diseased microenvironments, minimizing off-target effects. Specific use cases highlight their value: metformin prodrugs encapsulated in PLGA nanoparticles allow sustained release, overcoming its short half-life and gastrointestinal intolerance [34, 35]. Similarly, thiazolidinedione (TZD) drugs, notorious for fluid retention and systemic side effects, can be encapsulated in adipose-targeting micelles, concentrating activity in fat depots while sparing other tissues [36]. Polymeric carriers are also highly effective for nucleic acid delivery; siRNAs targeting negative regulators of insulin signaling, such as protein tyrosine phosphatase 1B (PTP1B) or lipogenesis driver SREBP-1c, can be shielded from degradation and delivered efficiently [37]. This combination of modular chemistry, biocompatibility, and multifunctionality makes polymeric nanoparticles and micelles indispensable in advancing precision therapy for metabolic diseases.

4.2 Lipid-Based Systems

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs), are among the most clinically validated platforms for drug delivery [22, 38]. Their biocompatibility, similarity to cellular membranes, and ability to encapsulate both hydrophilic and hydrophobic molecules make them highly attractive for antidiabetic applications. Liposomes, consisting of phospholipid bilayers, can encapsulate peptides such as GLP-1 analogs and exendin-4, protecting them from enzymatic degradation and prolonging their systemic half-life. SLNs and NLCs offer improved stability compared to traditional liposomes and can sustain drug release by embedding drugs within a lipid matrix [39–41]. Notably, LNPs have revolutionized nucleic acid delivery, as demonstrated by mRNA vaccines, and this success is now being extended to siRNA and antisense oligonucleotide (ASO) therapies targeting metabolic pathways in the liver. Liver-directed delivery can be further refined through ligand modifications, such as incorporating N-acetylgalactosamine (GalNAc) to exploit the asialoglycoprotein receptor (ASGPR) on hepatocytes, or by leveraging apolipoprotein exchange mechanisms to enrich hepatic uptake[42]. This makes LNPs especially powerful for silencing genes involved in lipogenesis or gluconeogenesis. Additionally, bile-salt-modified liposomes are being explored for oral formulations, enabling transit across the gastrointestinal mucus

barrier and improving bioavailability of peptide drugs. Such advances address one of the most significant challenges in diabetes therapy-developing oral or minimally invasive delivery systems for peptide hormones [43]. Overall, lipid-based systems combine clinical familiarity with cutting-edge adaptability, supporting both established therapies like insulin analogs and next-generation nucleic acid approaches for metabolic disease.

4.3 Inorganic and Hybrid Nanocarriers

Inorganic nanocarriers, such as mesoporous silica nanoparticles (MSNs), gold nanoparticles, and iron oxide nanostructures, bring unique advantages to metabolic disease therapeutics, particularly through their structural precision and multifunctionality [44]. MSNs, with their exceptionally high surface area and tunable pore sizes, can encapsulate a variety of molecules ranging from small drugs to biomacromolecules, allowing for controlled and sustained release. Gold nanoparticles are prized for their ability to act as photothermal agents, enabling externally triggered drug release under near-infrared (NIR) light, as well as for their surface chemistry, which facilitates ligand conjugation and nucleic acid delivery [45]. Iron oxide nanoparticles, on the other hand, offer magnetic responsiveness, enabling both targeted accumulation via magnetic guidance and imaging applications for theranostics. These inorganic systems, therefore, integrate therapy with diagnosis, advancing precision medicine in diabetes and obesity-related complications. However, significant challenges persist [46]. Many inorganic materials exhibit long-term persistence in the body and can accumulate in the reticuloendothelial system (RES), raising concerns about chronic toxicity. To address this, hybrid designs have emerged, combining inorganic cores with biodegradable or polymeric coatings that enhance clearance and biocompatibility[47]. Organosilica nanoparticles, for example, degrade more readily than conventional MSNs, while polymer-coated gold or iron oxide nanoparticles reduce immunogenicity and improve stability in circulation. Such hybrid systems balance functionality with safety, providing platforms that can deliver antidiabetic drugs or siRNA while allowing real-time imaging and external control[48]. Ultimately, while inorganic nanocarriers remain less clinically advanced than polymeric or lipid systems, their potential for multifunctional integration makes them valuable candidates for specialized metabolic interventions.

4.4 Biomimetic Platforms

Biomimetic nanocarriers, particularly exosomes and cell-membrane-coated nanoparticles, represent a cutting-edge strategy for enhancing drug delivery in diabetes and obesity-related disorders[30]. Exosomes are naturally secreted extracellular vesicles that mediate intercellular communication and inherently carry proteins, lipids, and nucleic acids. They possess innate tropism toward specific cell types, enabling selective targeting of tissues such as liver, adipose depots, and pancreatic islets[49]. Additionally, their endogenous origin allows them to evade rapid clearance by the immune system, prolonging circulation and improving therapeutic index. Similarly, nanoparticles cloaked with natural cell membranes derived from red blood cells, immune cells, or even adipocytes inherit the parent cell's surface markers, providing immune evasion, homing properties, and reduced nonspecific uptake[50]. These biomimetic strategies offer significant promise for delivering both conventional drugs and emerging payloads such as siRNA or CRISPR components, potentially enabling highly precise modulation of metabolic pathways. However, there are notable challenges that must be addressed before translation to the clinic. Exosomes are inherently heterogeneous, with variable cargo and targeting properties depending on their cellular origin, making standardization difficult[51]. Large-scale production and purification also remain technically challenging, hindering reproducibility. For membrane-coated nanoparticles, while the approach provides modularity and flexibility, regulatory frameworks for hybrid biologic–synthetic systems are still under development, adding another barrier. Nevertheless, the unique ability of biomimetic nanocarriers to combine natural biology with synthetic engineering positions them as a transformative platform for next-generation antidiabetic therapeutics, especially in scenarios where immune evasion and precision targeting are essential.

5. Targeting Strategies for Metabolic Organs

5.1 Passive vs. Active Targeting

Nanocarrier-based therapies for metabolic disorders rely heavily on strategies that determine where drugs accumulate in the body. Passive targeting leverages inherent physiological changes in obesity and diabetes, such as vascular inflammation, increased capillary permeability, and altered extracellular matrix composition in visceral adipose tissue and fatty liver[52]. While these changes are less pronounced than the enhanced permeability and retention (EPR) effect seen in tumors, they still provide opportunities for nanoparticles to preferentially accumulate in metabolically active tissues. For example, nanoparticles in the size range of 50–200 nm can penetrate inflamed adipose depots and hepatocytes to some degree, allowing a baseline level of enrichment without additional modifications[53]. However, this approach alone often results in limited specificity and significant off-target distribution. Active targeting addresses this limitation by decorating nanocarriers with ligands that engage receptor-mediated uptake pathways. These ligands include small molecules, peptides, sugars, and antibodies that bind selectively to receptors expressed on hepatocytes, adipocytes, β-cells, or immune cells involved in metaflammation. For instance, GalNAc ligands enable highly efficient uptake into hepatocytes via the asialoglycoprotein receptor, a strategy already validated in siRNA therapies[53]. Similarly, adipose-homing peptides and GLP-1 receptor-targeting ligands can direct nanoparticles to fat depots and pancreatic islets, respectively. By combining passive and active targeting, nanocarriers achieve dual benefits: leveraging vascular abnormalities to enter diseased tissue while using

receptor-specific interactions for precision uptake[54]. This hybrid strategy is particularly critical in metabolic diseases, where affected organs are diffuse and systemic, requiring highly discriminative delivery to minimize side effects. In practice, successful targeting strategies often integrate both approaches, ensuring robust accumulation in metabolic hubs while reducing systemic exposure and toxicity.

5.2 Organ/Tissue-Specific Hubs

The complexity of diabetes and obesity demands organ- and tissue-specific delivery approaches that align with the unique biology of each metabolic hub. The liver is a central regulator of glucose and lipid metabolism, making it an ideal target for RNA-based therapeutics. GalNAc-conjugated ligands are widely used to bind the asialoglycoprotein receptor on hepatocytes, enabling uptake of siRNA or antisense oligonucleotides designed to silence genes driving lipogenesis (e.g., SREBP-1c) or gluconeogenesis (e.g., G6PC)[55]. In adipose tissue, delivery is complicated by poor vascularization and depot expansion, but adipose-homing peptides such as those targeting prohibitin, as well as RGD motifs that bind angiogenic vasculature, enhance nanoparticle retention in fat depots. Hyaluronan can also direct nanoparticles to CD44 receptors on stromal cells and macrophages, enabling local modulation of inflammation[56]. Pancreatic β-cells are another critical focus; GLP-1 receptor-binding ligands derived from exendin or sulfonylurea-receptor motifs facilitate entry into islets. Since β-cells are tightly packed, particle size must remain below ~80 nm to allow efficient penetration. Immune cells play pivotal roles in metaflammation, and mannose-decorated nanoparticles exploit CD206 receptors on macrophages to selectively deliver anti-inflammatory payloads. Kupffer cells in the liver, accessible via scavenger receptor ligands, are another immunological gateway for modulating inflammation in nonalcoholic fatty liver disease (NAFLD) contexts[57]. Targeting skeletal muscle remains challenging, but transferrin and integrin-binding ligands have shown potential to increase uptake by myocytes, which could be harnessed for improving insulin sensitivity. Finally, the gut epithelium represents a novel frontier, with lectin-based targeting (UEA-I), vitamin B12/folate pathways, and mucoadhesive polymers such as chitosan enabling transport across mucus and M cells[58]. Collectively, these tissue-specific strategies illustrate how tailored targeting can unlock therapeutic efficacy across multiple interconnected organs in metabolic disease.

6.1 Glucose-Responsive Systems

Glucose-responsive nanocarriers represent a pioneering step toward achieving "closed-loop" insulin delivery, mimicking the physiological role of pancreatic β-cells. One of the most widely explored enzymatic approaches involves glucose oxidase (GOx), which catalyzes the conversion of glucose into gluconic acid[59]. This reaction lowers the local pH and triggers the breakdown of acid-sensitive matrices, resulting in on-demand insulin release. Such systems hold promise for achieving tighter glycemic control without continuous patient intervention. Another approach relies on chemical responsiveness, specifically phenylboronic acid (PBA), which binds reversibly to diol-containing molecules[60]. When glucose competes with PBA-crosslinked micelles or hydrogels, the network disassembles, releasing encapsulated insulin or other therapeutics. Lectin-based designs, most notably using concanavalin A, were among the earliest glucose-responsive concepts[60]. These exploit carbohydrate–protein interactions to modulate drug release but have fallen out of favor due to immunogenicity concerns. Despite this, newer biocompatible lectin-mimicking systems are under exploration. The key advantage of glucose-responsive carriers is their potential to create dynamic drug release proportional to real-time glucose fluctuations, reducing both hypoglycemia risk and patient burden. Integration with microneedle patches or implantable depots enhances their practicality, providing minimally invasive platforms for day-to-day diabetes management[61]. While clinical translation remains at an early stage, ongoing progress in polymer chemistry and biosensor integration suggests that glucose-responsive systems could one day transform diabetes care into a fully automated, patient-friendly process.

6.2 pH-, ROS-, and Enzyme-Responsive

Beyond glucose sensitivity, nanocarriers can exploit pathological hallmarks of diabetic tissues such as altered pH, oxidative stress, and elevated enzymatic activity. pH-responsive systems often employ enteric coatings that bypass stomach acid to enable oral peptide delivery[62]. Within target tissues, mildly acidic environments such as inflamed adipose tissue or fatty liver accelerate drug release from pH-labile linkers, ensuring localized therapy. Reactive oxygen species (ROS)-responsive designs are particularly valuable in obesity-driven inflammation, where elevated ROS levels degrade thioketal or boronic ester linkers, releasing drugs specifically in diseased microenvironments[63]. Enzyme-responsive systems provide an even finer level of specificity. Matrix metalloproteinases (MMPs), upregulated in adipose remodeling, lipases abundant in liver tissue, and glycosidases active in inflamed macrophages can all trigger cleavage of engineered linkers, liberating payloads directly at sites of pathology[63]. This strategy minimizes systemic toxicity by ensuring therapeutic activation only where disease-associated enzymes are present. By integrating these cues, nanocarriers effectively "sense" metabolic tissue states and tailor release accordingly. Such approaches are particularly advantageous for drugs with narrow therapeutic windows, including insulin sensitizers and RNA-based agents, where inappropriate systemic exposure could cause harm. Together, these stimuli-responsive platforms exemplify how nanomedicine can achieve spatiotemporally precise therapy by aligning drug release with microenvironmental pathology[64].

6.3 Externally Triggered Systems

Externally triggered drug release platforms add another layer of control to nanocarrier-based therapy, enabling on-demand activation by patients or clinicians. Thermal-responsive systems utilize temperature-sensitive

polymers that undergo phase transitions when heated, releasing their payload[65]. This can be paired with localized hyperthermia or external heating patches. Ultrasound provides a non-invasive trigger that induces cavitation or mechanical disruption of nanocarriers, accelerating drug release with high spatial precision. Magnetic nanoparticles offer the dual advantage of guidance and triggering, as alternating magnetic fields generate localized heating, promoting both drug release and targeted deposition in specific organs such as the liver[66]. Photothermal systems, particularly gold nanostructures activated by near-infrared (NIR) light, can similarly achieve localized release with millimeter-scale precision[67, 68]. These methods are especially suitable for depot-stored drugs placed subcutaneously or for catheter-assisted delivery to deeper tissues like the liver. A major advantage of externally triggered systems is their ability to synchronize therapy with fluctuating disease states or clinical interventions, providing flexibility and personalization[69]. However, practical limitations such as device availability, tissue penetration depth, and patient compliance must be addressed before widespread adoption. Nevertheless, the integration of external triggers with responsive nanocarriers illustrates the future potential for precision, patient-controlled drug delivery in metabolic disease.

7.1 Small-Molecule Antidiabetics

Nanocarrier systems are increasingly applied to enhance the pharmacokinetics and tolerability of small-molecule antidiabetic drugs. Metformin, the cornerstone therapy for type 2 diabetes, suffers from poor gastrointestinal absorption and dose-limiting GI intolerance[70]. Encapsulation within polymeric nanoparticles or micelles allows controlled release, reducing peak concentrations that cause side effects, while enabling once-daily or even targeted hepatic delivery to maximize efficacy at its site of action. Thiazolidinediones (TZDs), such as pioglitazone, activate PPARγ and improve insulin sensitivity but cause undesirable weight gain and fluid retention. By encapsulating TZDs in adipose-targeted nanoparticles, drug action can be restricted to fat depots, minimizing systemic exposure and adverse effects[71]. Similarly, SGLT2 inhibitors and DPP-4 inhibitors, both widely prescribed oral drugs, benefit from nanocarrier-based solubility enhancement[71]. Formulations that smooth drug absorption and prolong release can reduce glycemic variability and extend dosing intervals. Such improvements not only increase efficacy but also enhance adherence by lowering pill burden. Collectively, nanoparticle-based delivery reinvents established small molecules, extending their therapeutic life cycle and making them more patient-friendly.

7.2 Peptides and Proteins

Peptide- and protein-based drugs play a central role in diabetes therapy, but their fragility and short half-lives limit their utility. Insulin remains the most critical therapeutic, and nanocarrier innovations aim to eliminate the need for multiple daily injections[72]. Glucose-responsive microneedle patches and oral nanoparticles equipped with protease shields and permeation enhancers exemplify next-generation insulin delivery systems, providing noninvasive and self-regulating options. Depot hydrogels and injectable gels further enable sustained basal insulin release, reducing injection frequency. Beyond insulin, incretin-based therapies such as GLP-1, GIP, and amylin analogs are being revolutionized by nanocarriers that protect against proteolysis and improve systemic exposure[73]. Lipid and polymeric nanoparticles facilitate lymphatic uptake and enhance bioavailability, while combination delivery systems co-encapsulating GLP-1 analogs with small molecules like metformin provide synergistic glucose-lowering effects. By improving stability, extending half-life, and enabling noninvasive administration, nanocarriers are redefining how peptide drugs are integrated into long-term diabetes care[74].

7.3 Nucleic Acids and Gene Editing

Nanocarriers are indispensable for enabling nucleic acid therapeutics in diabetes, as naked siRNA, antisense oligonucleotides (ASOs), or mRNA are rapidly degraded and poorly internalized. Lipid nanoparticles (LNPs) and polymeric carriers provide protection and facilitate cellular uptake, allowing targeted silencing of genes central to glucose and lipid metabolism[75]. For example, siRNAs directed against SREBP-1c (lipogenesis) or G6PC (gluconeogenesis) can improve metabolic balance, while inhibition of PTP1B enhances insulin signaling. Beyond gene silencing, mRNA and CRISPR-based payloads are being explored for regenerative approaches, such as restoring β-cell function or reprogramming other pancreatic cells to produce insulin. These cutting-edge strategies demand strict biodistribution control to minimize off-target editing and immune activation, making nanocarriers essential[76]. Although still experimental, the promise of gene editing in diabetes underscores the need for sophisticated delivery platforms capable of balancing efficacy, safety, and precision.

7.4 Natural Products and Microbiome-Modulating Agents

Nanocarriers also open new avenues for natural products and microbiome-targeted therapies, which are increasingly recognized as modulators of metabolic health. Compounds such as berberine, curcumin, and resveratrol exhibit antidiabetic properties but suffer from poor solubility and rapid clearance[77]. Encapsulation into polymeric or lipid nanocarriers enhances solubility, improves intestinal retention, and allows localized activity in the gut, where many of their beneficial effects—such as modulation of bile acid signaling and short-chain fatty acid (SCFA) pathways—are most relevant[78]. Similarly, microbiome-targeted therapies including prebiotics, probiotics, and bile acid modulators benefit from colon-targeted delivery systems. pH-sensitive nanoparticles and enteric-coated capsules can protect these agents until they reach the colon, where they can reshape microbiota composition, enhance incretin release, and improve insulin sensitivity[79]. By enabling localized activity and reducing systemic side effects, nanocarriers make it feasible to harness natural compounds

and microbiome modulators as adjunctive therapies for diabetes. This emerging area exemplifies how nanomedicine bridges conventional pharmacology with systems-level metabolic regulation.

8. Future Directions and Open Questions

Organelle-level precision: Mitochondria-targeted antioxidants or UCP1 modulation for adipose browning without off-target thermogenesis.

Combinatorial payloads: Co-delivery (e.g., GLP-1 analog + amylin; siRNA + small molecule) with staggered release profiles.

Personalized targeting: Imaging-guided ligand selection based on a patient's hepatic fat fraction, depot distribution, and immune phenotype.

Adaptive/logic gating: AND/OR Boolean release requiring both high glucose and inflammatory ROS to prevent hypoglycemia.

Microbiome-aware delivery: Gut-retentive carriers that shape bile acid signaling and incretin tone with minimal systemic exposure.

Equity by design: Materials and processes that are scalable and affordable in low- and middle-income settings, where diabetes burden is rising fastest.

CONCLUSION

Smart nanocarriers can transform antidiabetic therapy in obesity by targeting the right tissues at the right time with the right payloads. Success will depend on marrying biological insight (tissue-specific receptors, pathophysiologic triggers) with manufacturable, safe, and user-friendly delivery formats. With careful attention to targeting fidelity, release control, and clinical practicality, these systems can substantially improve glycemic control and metabolic health while reducing treatment burden and side effects.

Abbreviations

ASGPR, asialoglycoprotein receptor; BAT, brown adipose tissue; CQAs, critical quality attributes; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GOx, glucose oxidase; GSIS, glucose-stimulated insulin secretion; LNP, lipid nanoparticle; MPS, mononuclear phagocyte system; MSN, mesoporous silica nanoparticle; NLC, nanostructured lipid carrier; PBA, phenylboronic acid; PD/PK, pharmacodynamics/pharmacokinetics; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PPARγ, peroxisome proliferator-activated receptor gamma; PTP1B, protein tyrosine phosphatase 1B; RES, reticuloendothelial system; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SGLT2, sodium-glucose cotransporter-2; siRNA, small interfering RNA; TZD, thiazolidinedione; UCP1, uncoupling protein 1; WAT, white adipose tissue.

REFERENCES

1. Hossain, Md.J., Al-Mamun, Md., Islam, Md.R.: Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Sci Rep. 7, e2004 (2024). https://doi.org/10.1002/hsr2.2004
2. Ahmed, B., Konje, J.C.: The epidemiology of obesity in reproduction. Best Practice & Research Clinical Obstetrics & Gynaecology. 89, 102342 (2023). https://doi.org/10.1016/j.bpobgyn.2023.102342
3. Allocca, S., Monda, A., Messina, A., Casillo, M., Sapuppo, W., Monda, V., Polito, R., Di Maio, G., Monda, M., La Marra, M.: Endocrine and Metabolic Mechanisms Linking Obesity to Type 2 Diabetes: Implications for Targeted Therapy. Healthcare. 13, 1437 (2025). https://doi.org/10.3390/healthcare13121437
4. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
5. Sharma, D., Arora, S., Banerjee, A., Singh, J.: Improved insulin sensitivity in obese-diabetic mice via chitosan Nanomicelles mediated silencing of pro-inflammatory Adipocytokines. Nanomedicine: Nanotechnology, Biology and Medicine. 33, 102357 (2021). https://doi.org/10.1016/j.nano.2020.102357
6. Fu, Y., Tang, R., Zhao, X.: Engineering cytokines for cancer immunotherapy: a systematic review. Front Immunol. 14, 1218082 (2023). https://doi.org/10.3389/fimmu.2023.1218082
7. Feingold, K.R.: Oral and Injectable (Non-Insulin) Pharmacological Agents for the Treatment of Type 2 Diabetes. In: Feingold, K.R., Ahmed, S.F., Anawalt, B., Blackman, M.R., Boyce, A., Chrousos, G., Corpas, E., de Herder, W.W., Dhatariya, K., Dungan, K., Hofland, J., Kalra, S., Kaltsas, G., Kapoor, N., Koch, C., Kopp, P., Korbonits, M., Kovacs, C.S., Kuohung, W., Laferrère, B., Levy, M., McGee, E.A., McLachlan, R., Muzumdar, R., Purnell, J., Rey, R., Sahay, R., Shah, A.S., Singer, F., Sperling, M.A., Stratakis, C.A., Trence, D.L., and Wilson, D.P. (eds.) Endotext. MDText.com, Inc., South Dartmouth (MA) (2000)
8. Gieroba, B., Kryska, A., Sroka-Bartnicka, A.: Type 2 diabetes mellitus – conventional therapies and future perspectives in innovative treatment. Biochemistry and Biophysics Reports. 42, 102037 (2025). https://doi.org/10.1016/j.bbrep.2025.102037
9. Triggle, C.R., Mohammed, I., Bshesh, K., Marei, I., Ye, K., Ding, H., MacDonald, R., Hollenberg, M.D., Hill, M.A.: Metformin: Is it a drug for all reasons and diseases? Metabolism. 133, 155223 (2022). https://doi.org/10.1016/j.metabol.2022.155223

10. Sultana, A., Zare, M., Thomas, V., Kumar, T.S.S., Ramakrishna, S.: Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects. Medicine in Drug Discovery. 15, 100134 (2022). https://doi.org/10.1016/j.medidd.2022.100134
11. Cheng, X., Xie, Q., Sun, Y.: Advances in nanomaterial-based targeted drug delivery systems. Front Bioeng Biotechnol. 11, 1177151 (2023). https://doi.org/10.3389/fbioe.2023.1177151
12. Qutub, M., Tatode, A., Iqbal, Z., Hussain, U.M., Taksande, J., Khan, R., Thakre, D., Premchandani, T., Umekar, M., Sheikh, S.: Stimuli-responsive nanovesicles for spatiotemporal control of drug delivery in chronic cutaneous wounds: Bridging molecular pathobiology to translational nanomedicine. Journal of Drug Delivery Science and Technology. 112, 107238 (2025). https://doi.org/10.1016/j.jddst.2025.107238
13. Sakers, A., De Siqueira, M.K., Seale, P., Villanueva, C.J.: Adipose-tissue plasticity in health and disease. Cell. 185, 419–446 (2022). https://doi.org/10.1016/j.cell.2021.12.016
14. Al-Jaber, H., Mohamed, N.A., Govindharajan, V.K., Taha, S., John, J., Halim, S., Alser, M., Al-Muraikhy, S., Anwardeen, N.R., Agouni, A., Elhissi, A., Al-Naemi, H.A., Al-Mansoori, L., Elrayess, M.A.: In Vitro and In Vivo Validation of GATA-3 Suppression for Induction of Adipogenesis and Improving Insulin Sensitivity. International Journal of Molecular Sciences. 23, 11142 (2022). https://doi.org/10.3390/ijms231911142
15. Al-Mansoori, L., Al-Jaber, H., Prince, M.S., Elrayess, M.A.: Role of Inflammatory Cytokines, Growth Factors and Adipokines in Adipogenesis and Insulin Resistance. Inflammation. 45, 31–44 (2022). https://doi.org/10.1007/s10753-021-01559-z
16. Jiang, S., Young, J.L., Wang, K., Qian, Y., Cai, L.: Diabetic-induced alterations in hepatic glucose and lipid metabolism: The role of type 1 and type 2 diabetes mellitus. Mol Med Rep. 22, 603–611 (2020). https://doi.org/10.3892/mmr.2020.11175
17. Willis, S.A., Bawden, S.J., Malaikah, S., Sargeant, J.A., Stensel, D.J., Aithal, G.P., King, J.A.: The role of hepatic lipid composition in obesity-related metabolic disease. Liver International. 41, 2819–2835 (2021). https://doi.org/10.1111/liv.15059
18. Herrera-Ojeda, J.L., Blanco-Palma, R.S., Chávez-Tapia, N.C., Uribe, M., Montalvo-Javé, E.E., Nuño-Lámbarri, N.: The pathophysiological link between type 1 diabetes and MASLD: insights into insulin resistance and liver dysfunction. J Endocrinol Invest. (2025). https://doi.org/10.1007/s40618-025-02621-5
19. Münte, E., Hartmann, P.: The Role of Short-Chain Fatty Acids in Metabolic Dysfunction-Associated Steatotic Liver Disease and Other Metabolic Diseases. Biomolecules. 15, 469 (2025). https://doi.org/10.3390/biom15040469
20. Masse, K.E., Lu, V.B.: Short-chain fatty acids, secondary bile acids and indoles: gut microbial metabolites with effects on enteroendocrine cell function and their potential as therapies for metabolic disease. Front Endocrinol (Lausanne). 14, 1169624 (2023). https://doi.org/10.3389/fendo.2023.1169624
21. Caturano, A., Nilo, R., Nilo, D., Russo, V., Santonastaso, E., Galiero, R., Rinaldi, L., Monda, M., Sardu, C., Marfella, R., Sasso, F.C.: Advances in Nanomedicine for Precision Insulin Delivery. Pharmaceuticals (Basel). 17, 945 (2024). https://doi.org/10.3390/ph17070945
22. Plaza-Oliver, M., Santander-Ortega, M.J., Lozano, M.Victoria.: Current approaches in lipid-based nanocarriers for oral drug delivery. Drug Deliv Transl Res. 11, 471–497 (2021). https://doi.org/10.1007/s13346-021-00908-7
23. Hoang Thi, T.T., Pilkington, E.H., Nguyen, D.H., Lee, J.S., Park, K.D., Truong, N.P.: The Importance of Poly(ethylene glycol) Alternatives for Overcoming PEG Immunogenicity in Drug Delivery and Bioconjugation. Polymers (Basel). 12, 298 (2020). https://doi.org/10.3390/polym12020298
24. Tsuchiya, K., Horikoshi, K., Fujita, M., Hirano, M., Miyamoto, M., Yokoo, H., Demizu, Y.: Development of Hydrophobic Cell-Penetrating Stapled Peptides as Drug Carriers. Int J Mol Sci. 24, 11768 (2023). https://doi.org/10.3390/ijms241411768
25. Wells, C.M., Harris, M., Choi, L., Murali, V.P., Guerra, F.D., Jennings, J.A.: Stimuli-Responsive Drug Release from Smart Polymers. J Funct Biomater. 10, 34 (2019). https://doi.org/10.3390/jfb10030034
26. Singh, N., Marets, C., Boudon, J., Millot, N., Saviot, L., Maurizi, L.: In vivo protein corona on nanoparticles: does the control of all material parameters orient the biological behavior? Nanoscale Adv. 3, 1209–1229. https://doi.org/10.1039/d0na00863j
27. Bernal-Chávez, S.A., Del Prado-Audelo, M.L., Caballero-Florán, I.H., Giraldo-Gomez, D.M., Figueroa-Gonzalez, G., Reyes-Hernandez, O.D., González-Del Carmen, M., González-Torres, M., Cortés, H., Leyva-Gómez, G.: Insights into Terminal Sterilization Processes of Nanoparticles for Biomedical Applications. Molecules. 26, 2068 (2021). https://doi.org/10.3390/molecules26072068
28. Wu, J., Yan, D., Du, X., Chen, W., Lin, X., Xu, B., Xu, Y., Ye, J., Shen, Y.: AI-driven Design of Drug Delivery Systems: Strategies and Challenges in Overcoming Biological Barriers. Acta Pharmaceutica Sinica B. (2025). https://doi.org/10.1016/j.apsb.2025.06.010
29. Uti, D.E., Atangwho, I.J., Alum, E.U., Ntaobeten, E., Obeten, U.N., Bawa, I., Agada, S.A., Ukam, C.I.-O., Egbung, G.E.: Antioxidants in cancer therapy mitigating lipid peroxidation without compromising

treatment through nanotechnology. Discover Nano. 20, 70 (2025). https://doi.org/10.1186/s11671-025-04248-0
30. Uti, D.E., Alum, E.U., Atangwho, I.J., Ugwu, O.P.-C., Egbung, G.E., Aja, P.M.: Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. Journal of Nanobiotechnology. 23, 336 (2025). https://doi.org/10.1186/s12951-025-03412-z
31. kapoor, D. u, Garg, R., Gaur, M., Prajapati, B.G., Agrawal, G., Bhattacharya, S., Elossaily, G.M.: Polymeric nanoparticles approach and identification and characterization of novel biomarkers for colon cancer. Results in Chemistry. 6, 101167 (2023). https://doi.org/10.1016/j.rechem.2023.101167
32. Wang, X.-Q., Zhang, Q.: pH-sensitive polymeric nanoparticles to improve oral bioavailability of peptide/protein drugs and poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 82, 219–229 (2012). https://doi.org/10.1016/j.ejpb.2012.07.014
33. Hou, J., Xue, Z., Chen, Y., Li, J., Yue, X., Zhang, Y., Gao, J., Hao, Y., Shen, J.: Development of Stimuli-Responsive Polymeric Nanomedicines in Hypoxic Tumors and Their Therapeutic Promise in Oral Cancer. Polymers. 17, 1010 (2025). https://doi.org/10.3390/polym17081010
34. Ghandforoushan, P., Hanaee, J., Aghazadeh, Z., Samiei, M., Navali, A.M., Khatibi, A., Davaran, S.: Enhancing the function of PLGA-collagen scaffold by incorporating TGF-β1-loaded PLGA-PEG-PLGA nanoparticles for cartilage tissue engineering using human dental pulp stem cells. Drug Deliv Transl Res. 12, 2960–2978 (2022). https://doi.org/10.1007/s13346-022-01161-2
35. Omidian, H., Wilson, R.L., Castejon, A.M.: Recent Advances in Peptide-Loaded PLGA Nanocarriers for Drug Delivery and Regenerative Medicine. Pharmaceuticals. 18, 127 (2025). https://doi.org/10.3390/ph18010127
36. Zhang, F., Pan, X., Zhang, X., Tong, N.: The effect of thiazolidinediones on body fat redistribution in adults: A systematic review and meta-analysis of randomized controlled trials. Obes Rev. 25, e13675 (2024). https://doi.org/10.1111/obr.13675
37. Owen, C., Czopek, A., Agouni, A., Grant, L., Judson, R., Lees, E.K., Mcilroy, G.D., Göransson, O., Welch, A., Bence, K.K., Kahn, B.B., Neel, B.G., Mody, N., Delibegović, M.: Adipocyte-Specific Protein Tyrosine Phosphatase 1B Deletion Increases Lipogenesis, Adipocyte Cell Size and Is a Minor Regulator of Glucose Homeostasis. PLOS ONE. 7, e32700 (2012). https://doi.org/10.1371/journal.pone.0032700
38. Kumar, R., Dkhar, D.S., Kumari, R., Divya, Mahapatra, S., Srivastava, A., Dubey, V.K., Chandra, P.: Ligand conjugated lipid-based nanocarriers for cancer theranostics. Biotechnology and Bioengineering. 119, 3022–3043 (2022). https://doi.org/10.1002/bit.28205
39. Abbasi, H., Kouchak, M., Mirveis, Z., Hajipour, F., Khodarahmi, M., Rahbar, N., Handali, S.: What We Need to Know about Liposomes as Drug Nanocarriers: An Updated Review. Adv Pharm Bull. 13, 7–23 (2023). https://doi.org/10.34172/apb.2023.009
40. Rao, L., Zhu, P., Guo, M., Hu, M., Guo, X., Du, Y., Xu, G.: Nebulized inhalation of nintedanib-loaded biomimetic nano-liposomes attenuated bleomycin-induced interstitial lung fibrosis in mice. Nano Today. 56, 102298 (2024). https://doi.org/10.1016/j.nantod.2024.102298
41. Wang, S., Chen, Y., Guo, J., Huang, Q.: Liposomes for Tumor Targeted Therapy: A Review. Int J Mol Sci. 24, 2643 (2023). https://doi.org/10.3390/ijms24032643
42. Arjunan, P., Kathirvelu, D., Mahalingam, G., Goel, A.K., Zacharaiah, U.G., Srivastava, A., Marepally, S.: Lipid-nanoparticle-enabled nucleic acid therapeutics for liver disorders. Acta Pharm Sin B. 14, 2885–2900 (2024). https://doi.org/10.1016/j.apsb.2024.04.015
43. Suri, K., Pfeifer, L., Cvet, D., Li, A., McCoy, M., Singh, A., Amiji, M.M.: Oral delivery of stabilized lipid nanoparticles for nucleic acid therapeutics. Drug Deliv Transl Res. 15, 1755–1769 (2025). https://doi.org/10.1007/s13346-024-01709-4
44. Yanar, F., Carugo, D., Zhang, X.: Hybrid Nanoplatforms Comprising Organic Nanocompartments Encapsulating Inorganic Nanoparticles for Enhanced Drug Delivery and Bioimaging Applications. Molecules. 28, 5694 (2023). https://doi.org/10.3390/molecules28155694
45. Magadani, R., Ndinteh, D.T., Roux, S., Nangah, L.P., Atangwho, I.J., Uti, D.E., Alum, E.U., Egba, S.I.: Cytotoxic Effects of Lecaniodiscus Cupanioides (Planch.) Extract and Triterpenoids-derived Gold Nanoparticles On MCF-7 Breast Cancer Cell Lines. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry - Anti-Cancer Agents). 25, 841–850 (2025). https://doi.org/10.2174/0118715206325529241004064307
46. Dadfar, S.M., Roemhild, K., Drude, N.I., von Stillfried, S., Knüchel, R., Kiessling, F., Lammers, T.: Iron Oxide Nanoparticles: Diagnostic, Therapeutic and Theranostic Applications. Adv Drug Deliv Rev. 138, 302–325 (2019). https://doi.org/10.1016/j.addr.2019.01.005
47. Chehelgerdi, M., Chehelgerdi, M., Allela, O.Q.B., Pecho, R.D.C., Jayasankar, N., Rao, D.P., Thamaraikani, T., Vasanthan, M., Viktor, P., Lakshmaiya, N., Saadh, M.J., Amajd, A., Abo-Zaid, M.A., Castillo-Acobo, R.Y., Ismail, A.H., Amin, A.H., Akhavan-Sigari, R.: Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Mol Cancer. 22, 169 (2023). https://doi.org/10.1186/s12943-023-01865-0

48. Santhamoorthy, M., Asaithambi, P., Ramkumar, V., Elangovan, N., Perumal, I., Kim, S.C.: A Review on the Recent Advancements of Polymer-Modified Mesoporous Silica Nanoparticles for Drug Delivery Under Stimuli-Trigger. Polymers. 17, 1640 (2025). https://doi.org/10.3390/polym17121640
49. Macário-Soares, A., Sousa-Oliveira, I., Correia, M., Pires, P.C., Sharma, A., Kumar Jha, N., Zare, E.N., Veiga, F., Gowda, B.H.J., Borzacchiello, A., Sethi, G., Makvandi, P., Paiva-Santos, A.C.: Cell membrane and extracellular vesicle membrane-coated nanoparticles: An envisaged approach for the management of skin conditions. VIEW. 5, 20240043 (2024). https://doi.org/10.1002/VIW.20240043
50. Hoffman, A., Nizet, V.: The Prospect of Biomimetic Immune Cell Membrane-Coated Nanomedicines for Treatment of Serious Bacterial Infections and Sepsis. J Pharmacol Exp Ther. 389, 289–300 (2024). https://doi.org/10.1124/jpet.123.002095
51. Dubey, A.K., Mostafavi, E.: Biomaterials-mediated CRISPR/Cas9 delivery: recent challenges and opportunities in gene therapy. Front Chem. 11, 1259435 (2023). https://doi.org/10.3389/fchem.2023.1259435
52. Cong, X., Zhang, Z., Li, H., Yang, Y.-G., Zhang, Y., Sun, T.: Nanocarriers for targeted drug delivery in the vascular system: focus on endothelium. J Nanobiotechnology. 22, 620 (2024). https://doi.org/10.1186/s12951-024-02892-9
53. Sibuyi, N.R.S., Moabelo, K.L., Meyer, M., Onani, M.O., Dube, A., Madiehe, A.M.: Nanotechnology advances towards development of targeted-treatment for obesity. Journal of Nanobiotechnology. 17, 122 (2019). https://doi.org/10.1186/s12951-019-0554-3
54. Luo, T., Chen, L., Tu, K., Jiang, L., Liang, S., Wang, S., Huang, Y., Yang, X.: Adipose tissue-targeted drug delivery for treating obesity: current opportunities and challenges. Drug Deliv. 32, 2547751. https://doi.org/10.1080/10717544.2025.2547751
55. Debacker, A.J., Voutila, J., Catley, M., Blakey, D., Habib, N.: Delivery of Oligonucleotides to the Liver with GalNAc: From Research to Registered Therapeutic Drug. Mol Ther. 28, 1759–1771 (2020). https://doi.org/10.1016/j.ymthe.2020.06.015
56. Uti, D.E., Omang, W.A., Alum, E.U., Ugwu, O.P.-C., Wokoma, M.A., Oplekwu, R.I., Atangwho, I.J., Egbung, G.E.: Combined Hyaluronic Acid Nanobioconjugates Impair CD44-Signaling for Effective Treatment Against Obesity: A Review of Comparison with Other Actors. Int J Nanomedicine. 20, 10101–10126 (2025). https://doi.org/10.2147/IJN.S529250
57. Fang, Z., Chen, S., Manchanda, Y., Bitsi, S., Pickford, P., David, A., Shchepinova, M.M., Corrêa Jr, I.R., Hodson, D.J., Broichhagen, J., Tate, E.W., Reimann, F., Salem, V., Rutter, G.A., Tan, T., Bloom, S.R., Tomas, A., Jones, B.: Ligand-Specific Factors Influencing GLP-1 Receptor Post-Endocytic Trafficking and Degradation in Pancreatic Beta Cells. International Journal of Molecular Sciences. 21, 8404 (2020). https://doi.org/10.3390/ijms21218404
58. Aleksandrowicz, R., Strączkowski, M.: Link between insulin resistance and skeletal muscle extracellular matrix remodeling. Endocr Connect. 12, e230023 (2023). https://doi.org/10.1530/EC-23-0023
59. Wang, J., Wang, Z., Yu, J., Kahkoska, A.R., Buse, J.B., Gu, Z.: Glucose-responsive insulin and delivery systems: innovation and translation. Adv Mater. 32, e1902004 (2020). https://doi.org/10.1002/adma.201902004
60. Pal, S., Rakshit, T., Saha, S., Jinagal, D.: Glucose-Responsive Materials for Smart Insulin Delivery: From Protein-Based to Protein-Free Design. ACS Mater Au. 5, 239–252 (2025). https://doi.org/10.1021/acsmaterialsau.4c00138
61. Baral, K.C., Choi, K.Y.: Barriers and Strategies for Oral Peptide and Protein Therapeutics Delivery: Update on Clinical Advances. Pharmaceutics. 17, 397 (2025). https://doi.org/10.3390/pharmaceutics17040397
62. Li, M., Wang, N., Liu, R., Zhang, X., He, W., Zhang, W., Li, J., Peng, C., Li, Y.: pH and H2O2 dual-sensitive nanoparticles enable enhanced and safe glucose-responsive oral insulin delivery for diabetes mellitus treatment. Theranostics. 14, 5596–5607 (2024). https://doi.org/10.7150/thno.98177
63. Yang, J., des Rieux, A., Malfanti, A.: Stimuli-Responsive Nanomedicines for the Treatment of Non-cancer Related Inflammatory Diseases. ACS Nano. 19, 15189–15219 (2025). https://doi.org/10.1021/acsnano.5c00700
64. Du, H., Xu, T., Yu, S., Wu, S., Zhang, J.: Mitochondrial metabolism and cancer therapeutic innovation. Signal Transduct Target Ther. 10, 245 (2025). https://doi.org/10.1038/s41392-025-02311-x
65. Karimi, M., Zangabad, P.S., Ghasemi, A., Amiri, M., Bahrami, M., Malekzad, H., Asl, H.G., Mahdieh, Z., Bozorgomid, M., Ghasemi, A., Boyuk, M.R.R.T., Hamblin, M.R.: Temperature-Responsive Smart Nanocarriers for Delivery Of Therapeutic Agents: Applications and Recent Advances. ACS Appl Mater Interfaces. 8, 21107–21133 (2016). https://doi.org/10.1021/acsami.6b00371
66. Chen, Y., Sun, H., Li, Y., Han, X., Yang, Y., Chen, Z., Zhao, X., Qian, Y., Liu, X., Zhou, F., Bai, J., Qiao, Y.: Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Bioactive Materials. 53, 591–629 (2025). https://doi.org/10.1016/j.bioactmat.2025.07.033

67. Beniwal, N., Verma, A., Putta, C.L., Rengan, A.K.: Recent Trends in Bio-nanomaterials and Non-invasive Combinatorial Approaches of Photothermal Therapy against Cancer. Nanotheranostics. 8, 219–238 (2024). https://doi.org/10.7150/ntno.91356
68. Nassireslami, E., Ajdarzade, M.: Gold Coated Superparamagnetic Iron Oxide Nanoparticles as Effective Nanoparticles to Eradicate Breast Cancer Cells via Photothermal Therapy. Adv Pharm Bull. 8, 201–209 (2018). https://doi.org/10.15171/apb.2018.024
69. Han, H.S., Choi, K.Y.: Advances in Nanomaterial-Mediated Photothermal Cancer Therapies: Toward Clinical Applications. Biomedicines. 9, 305 (2021). https://doi.org/10.3390/biomedicines9030305
70. Sarkhel, S., Shuvo, S.M., Ansari, M.A., Mondal, S., Kapat, P., Ghosh, A., Sarkar, T., Biswas, R., Atanase, L.I., Carauleanu, A.: Nanotechnology-Based Approaches for the Management of Diabetes Mellitus: An Innovative Solution to Long-Lasting Challenges in Antidiabetic Drug Delivery. Pharmaceutics. 16, 1572 (2024). https://doi.org/10.3390/pharmaceutics16121572
71. Liu, M., Wang, R., Hoi, M.P.M., Wang, Y., Wang, S., Li, G., Vong, C.T., Chong, C.-M.: Nano-Based Drug Delivery Systems for Managing Diabetes: Recent Advances and Future Prospects. Int J Nanomedicine. 20, 6221–6252 (2025). https://doi.org/10.2147/IJN.S508875
72. Ding, B., Zhu, Z., Guo, C., Li, J., Gan, Y., Yu, M.: Oral peptide therapeutics for diabetes treatment: State-of-the-art and future perspectives. Acta Pharmaceutica Sinica B. 14, 2006–2025 (2024). https://doi.org/10.1016/j.apsb.2024.02.019
73. Zhao, J., Xu, G., Yao, X., Zhou, H., Lyu, B., Pei, S., Wen, P.: Microneedle-based insulin transdermal delivery system: current status and translation challenges. Drug Deliv Transl Res. 12, 2403–2427 (2022). https://doi.org/10.1007/s13346-021-01077-3
74. Simos, Y.V., Spyrou, K., Patila, M., Karouta, N., Stamatis, H., Gournis, D., Dounousi, E., Peschos, D.: Trends of nanotechnology in type 2 diabetes mellitus treatment. Asian J Pharm Sci. 16, 62–76 (2021). https://doi.org/10.1016/j.ajps.2020.05.001
75. Niculescu, A.-G., Bîrcă, A.C., Grumezescu, A.M.: New Applications of Lipid and Polymer-Based Nanoparticles for Nucleic Acids Delivery. Pharmaceutics. 13, 2053 (2021). https://doi.org/10.3390/pharmaceutics13122053
76. DeBose-Boyd, R.A., Ye, J.: SREBPs in Lipid Metabolism, Insulin Signaling, and Beyond. Trends Biochem Sci. 43, 358–368 (2018). https://doi.org/10.1016/j.tibs.2018.01.005
77. Uti, D.E., Atangwho, I.J., Alum, E.U., Egba, S.I., Ugwu, O.P.-C., Ikechukwu, G.C.: Natural Antidiabetic Agents: Current Evidence and Development Pathways from Medicinal Plants to Clinical use. Natural Product Communications. 20, 1934578X251323393 (2025). https://doi.org/10.1177/1934578X251323393
78. Edo, G.I., Mafe, A.N., Razooqi, Nawar.F., Umelo, E.C., Gaaz, T.S., Isoje, E.F., Igbuku, U.A., Akpoghelie, P.O., Opiti, R.A., Essaghah, A.E.A., Ahmed, D.S., Umar, H., Ozsahin, D.U.: Advances in bio-polymer coatings for probiotic microencapsulation: chitosan and beyond for enhanced stability and controlled release. Des Monomers Polym. 28, 1–34. https://doi.org/10.1080/15685551.2024.2448122
79. Zhao, L., Niu, M., Ma, Z., He, F., Liu, X., Gong, X., Chai, Z., Wang, Z., Feng, Q., Wang, L.: Modified probiotics and the related combinatorial therapeutics. Acta Pharm Sin B. 15, 2431–2453 (2025). https://doi.org/10.1016/j.apsb.2025.03.021

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