Research Output Journal of Biological and Applied Science 6(1):11-18, 2026

ROJBAS Publications ONLINE ISSN: 1115-9200

https://rojournals.org/roj-biological-and-applied-science/ PRINT ISSN: 1115-6120

https://doi.org/10.59298/ROJBAS/2026/611118

Targeted Nanocarriers for Insulin and Incretin Delivery: Overcoming Barriers in Type 2 Diabetes Management

Mugisha Emmanuel K.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Type 2 diabetes (T2D) is driven by insulin resistance, β-cell dysfunction, and impaired incretin biology. While subcutaneous insulin and incretin-based therapies have transformed glycemic care, real-world effectiveness is limited by hypoglycemia, gastrointestinal side effects, variable absorption, and adherence barriers related to injection burden. Targeted nanocarriers offer a strategy to enhance therapeutic index by improving stability, depot residence, and tissue-selective delivery of peptide hormones. Nanoparticles can shield insulin and incretin mimetics from enzymatic degradation, traverse mucosal barriers, exploit lymphatic transport, and release cargo in response to stimuli such as glucose, pH, enzymes, or redox gradients. Ligand-directed systems further bias biodistribution toward hepatocytes, adipose, or muscle to better recapitulate physiologic insulin gradients, while depot-forming formulations can provide steady exposure with reduced peak–trough fluctuation. This review surveys the biological and biophysical barriers that shape hormone delivery; design rules for lipid, polymer, and hybrid nanocarriers; advances in oral, pulmonary, transdermal, and intraperitoneal routes; and smart glucose-responsive platforms enabling closed-loop–like control. We discuss safety, manufacturing, and regulatory considerations, and outline clinically pragmatic trial designs that integrate pharmacokinetics with continuous glucose monitoring and hypoglycemia endpoints. By aligning material science with endocrine physiology, targeted nanocarriers can make insulin and incretin therapy safer, more precise, and easier to live with.

Keywords: insulin delivery; GLP-1; GIP; nanomedicine; oral peptides; targeted nanoparticles; glucose-responsive systems; lymphatic transport; hepatic targeting; type 2 diabetes

INTRODUCTION

Type 2 diabetes emerges from the confluence of insulin resistance in the liver and skeletal muscle, progressive β-cell stress, and alterations in enteroendocrine signaling[1–3]. Exogenous insulin remains indispensable for many people with T2D to achieve glucose targets, and incretin-based drugs—GLP-1 receptor agonists and dual GLP-1/GIP co-agonists have reshaped treatment by lowering glucose, promoting weight loss, and improving cardiovascular outcomes. Nevertheless, current delivery paradigms impose trade-offs. Subcutaneous administration creates nonphysiologic exposure patterns, with systemic peaks that can induce hypoglycemia or nausea and with depot kinetics that vary by site, temperature, and activity[4–6]. Peptide instability, enzymatic degradation, and permeability barriers complicate oral administration, and the injection burden undermines adherence, particularly when multi-daily dosing or titration is required. These challenges motivate technologies that not only improve convenience but also respect endocrine physiology.

Nanotechnology provides a versatile platform to address these needs. At the most basic level, nanoparticles protect fragile peptides from proteases and denaturation. Beyond protection, they can be engineered for targeted delivery, controlled release, and stimuli-responsiveness[7–10]. Lipid nanoparticles, polymeric micelles, dendrimers, and inorganic–organic hybrids can encapsulate insulin, GLP-1 analogs, or co-agonists, preserving bioactivity while modulating pharmacokinetics. Surface functionalization with ligands that recognize intestinal M cells, transcytosis receptors, hepatocyte asialoglycoprotein receptors, or adipose endothelium can guide where and how hormones distribute after administration. For oral delivery, mucoadhesive coatings, permeation enhancers, and pH-responsive shells help nanoparticles survive gastric transit, adhere to intestinal epithelium, and exploit lymphatic uptake that bypasses first-pass degradation[11, 12]. For parenteral routes, nanocarriers

can create long-acting depots, smooth absorption kinetics, and localize exposure to targeted tissues, potentially widening the therapeutic window.

Physiology offers a blueprint. Endogenous insulin secreted into the portal circulation first acts on hepatocytes to suppress gluconeogenesis and regulate glycogen flux; peripheral tissues encounter a lower insulin concentration. By contrast, subcutaneous insulin delivers higher peripheral than portal levels, skewing the balance toward muscle and adipose while leaving liver relatively under-dosed[13–15]. Nanocarriers that preferentially deliver insulin to the liver or that release insulin in response to local glucose elevations could reestablish a more physiologic gradient and reduce peripheral hypoglycemia. Incretin pharmacology also benefits from targeting. GLP-1 receptor agonists act centrally and peripherally to slow gastric emptying, suppress appetite, and enhance glucose-dependent insulin secretion, but high systemic peaks can exacerbate nausea. Depot or tissue-selective delivery that restrains peak exposure may retain metabolic benefits while improving tolerability.

Smart, glucose-responsive systems represent a particularly promising frontier. By integrating glucose oxidase or phenylboronic acid motifs, nanoparticles can sense hyperglycemia and modulate insulin release accordingly, approximating the dynamic control achieved by closed-loop pumps without hardware[14, 16, 17]. Redox-, enzyme-, and temperature-responsive designs add further layers of control, enabling on-demand release aligned with metabolic state. Critically, these materials must operate within the safety constraints of chronic therapy: minimal immunogenicity, predictable manufacturing under GMP, and compatibility with re-dosing.

Translation requires rigorous evaluation that goes beyond blood glucose snapshots. Continuous glucose monitoring (CGM) provides high-resolution metrics, time in range, hypoglycemia burden, glycemic variability that are well suited for dose optimization of novel delivery systems[18, 19]. Pharmacokinetic and pharmacodynamic studies should quantify portal versus peripheral surrogates where feasible, and imaging or tracer methodologies can probe organ-specific exposure. Safety assessments need to account for complement activation, anti-polymer antibodies, and local tissue responses at administration sites[19].

This review integrates materials engineering, mucosal and vascular biology, and clinical pharmacology to examine how targeted nanocarriers can overcome long-standing barriers in insulin and incretin therapy. We first define the barriers that shape absorption and distribution, then outline design principles for stable, targeted, and responsive carriers. We examine oral and alternative routes with an emphasis on systems that deliver meaningful bioavailability and physiologic targeting. We conclude with a translational roadmap that prioritizes patient-centered outcomes, fewer injections, less hypoglycemia, and improved tolerability while aligning with regulatory expectations. The overarching thesis is that targeted nanocarriers can decouple efficacy from side effects, moving peptide endocrinology toward precision delivery.

2. Biological Barriers and Pharmacology Constraints Shaping Delivery Systems

The gastrointestinal tract poses multilayered obstacles to peptide delivery: acidic gastric pH, proteases such as pepsin and trypsin, mucus turnover, tight junctions limiting paracellular passage, and efflux transporters. Nanocarriers must therefore buffer pH, inhibit or evade proteolysis, adhere to or penetrate mucus, and traverse epithelia without provoking inflammation[20]. Enteric coatings protect in the stomach and dissolve in the small intestine; mucoadhesive polymers increase residence time but can impede movement, necessitating a balance between adhesion and penetration. Transcytosis through M cells in Peyer's patches or receptor-mediated transport via neonatal Fc receptor and transferrin receptor are promising entry routes; however, competition with endogenous ligands and receptor saturation must be considered[20]. Lymphatic uptake offers a path to systemic circulation while partially bypassing hepatic first pass, though for insulin a portal-first delivery may be preferred, requiring innovative routing strategies.

For parenteral routes, the subcutaneous space introduces variability due to local blood flow, temperature, and enzymatic milieu. Nanocarriers can modulate this environment by forming in situ depots or by responding to interstitial cues[21]. Yet the reticuloendothelial system, liver and spleen macrophages clear circulating particles, particularly those with positive surface charge or larger hydrodynamic size. Stealth coatings reduce opsonization but may provoke anti-PEG antibodies upon repeated dosing, altering pharmacokinetics and tolerability. Complement activation–related pseudoallergy is a specific risk for certain lipid and polymer chemistries[21].

Pharmacology imposes its own constraints. Insulin's rapid on/off dynamics are essential for postprandial control but risky when mismatched to meal timing. Incretins act in a glucose-dependent manner, offering safety against hypoglycemia but causing dose-limiting gastrointestinal effects at high peaks[22]. Therefore, delivery systems should target a Goldilocks zone: rapid enough to manage meals, stable enough to avoid peaks and troughs, and targeted enough to reduce off-target receptor activation. Co-delivery of enzymes or permeation enhancers raises regulatory complexity and safety concerns; hence, intrinsic material properties that achieve the same ends are preferable[22].

Finally, patient heterogeneity matters. Adiposity alters lymphatic flow, subcutaneous physiology, and tissue perfusion; gastroparesis changes gastric emptying; chronic inflammation modifies macrophage function and nanoparticle clearance. Delivery systems must perform robustly across these variables, and clinical trials should stratify by factors such as BMI, gastric motility, and baseline hypoglycemia risk[23]. Addressing these barriers

and constraints in the design phase improves the chance that promising preclinical performance translates to real-world benefit.

3. Design Principles of Nanocarriers for Hormone and Peptide Delivery

Effective nanocarriers harmonize composition, architecture, and surface chemistry with the demands of the intended route and target tissue. Lipid nanoparticles and solid lipid particles offer high peptide encapsulation efficiency and biocompatibility; ionizable lipids facilitate endosomal escape where intracellular delivery is needed, whereas more inert matrices suit extracellular release[10, 24–26]. Polymeric systems such as PLGA, poly(ortho esters), and poly(β-amino esters) provide tunable degradation kinetics from days to months, enabling depot formation. Hydrogels and in situ–gelling systems create macroscopic depots of nanoscale domains, delivering near–zero-order release for long-acting incretins[27–29].

Surface functionalization drives targeting and barrier crossing. For oral delivery, chitosan derivatives open tight junctions transiently and confer mucoadhesion; zwitterionic coatings resist mucus entanglement and protein fouling[30]. Ligands such as RGD peptides, galactose, N-acetylgalactosamine, transferrin, and Fc fragments can engage transport pathways. In the liver, asialoglycoprotein receptor ligands enrich hepatocyte exposure, whereas apolipoprotein E adsorption promotes LDL receptor–mediated uptake. In muscle and adipose, integrin-binding motifs and caveolae-targeting peptides may enhance trans-endothelial passage[30].

Release control is integral. Diffusion-dominated release risks burst kinetics and hypoglycemia for insulin; combining crystallinity control, core–shell architectures, and responsive linkers tempers the initial burst[31]. Enzyme-labile linkers responsive to intestinal or interstitial enzymes, pH-sensitive acetal or orthoester bonds, and redox-cleavable disulfides enable context-aware delivery. For co-encapsulation of insulin with a GLP-1 analog, orthogonal compartments or differential linker sensitivities can orchestrate staggered release, approximating physiologic sequence where incretin signal precedes insulin peak.

Analytics and manufacturability determine clinical viability. Microfluidic or in-line nanoprecipitation yields narrow size distributions and reproducible payload loading. Critical quality attributes include particle size, polydispersity, zeta potential, residual solvent, peptide integrity, and in vitro–in vivo correlation of release[32]. Stability programs should assess aggregation, hydrolysis, and peptide oxidation under refrigerated and accelerated conditions, with protective excipients such as sugars and amino acids. Sterility assurance and low endotoxin levels are mandatory for injectables, and enteric products must withstand simulated gastric and intestinal fluids[32].

Finally, usability cannot be an afterthought. Viscosity and syringeability affect patient experience; patch compatibility and pen devices influence adherence. For oral formulations, capsule size and food effects must be addressed. The best nanocarrier is not only elegant in vitro but also manufacturable, stable on the shelf, and simple for patients and clinicians to use in the messiness of everyday life.

4. Oral and Gastrointestinal Routes: Mucoadhesive, Lymphotropic, and M-Cell–Targeted Systems

Oral delivery of peptides is a long-standing goal because it promises painless administration and high acceptance. Nanocarriers help by coordinating protection, adhesion, penetration, and uptake. Enteric-coated capsules shield contents from gastric acid, releasing nanoparticles in the small intestine where pH rises[16, 16, 33, 34]. Within this window, mucoadhesive shells often chitosan, thiolated polymers, or carbomers anchor particles to the mucus layer, increasing local concentration. Yet excessive adhesion traps particles in rapidly cleared mucus; thus, mucus-inert inner layers or “slippery” zwitterionic brushes can assist penetration to the epithelium.

Trans-epithelial transport proceeds through two broad routes: paracellular and transcellular. Tight-junction modulation via chitosan derivatives or calcium chelation transiently widens paracellular spaces but must avoid compromising barrier function. For transcellular transport, receptor-mediated transcytosis is preferred[35]. Decorating nanoparticles with ligands for M cell receptors or neonatal Fc receptor promotes transport across follicle-associated epithelium. Once past the epithelium, lymphatic uptake can deliver cargo into systemic circulation while limiting hepatic first-pass degradation. Lipid-rich particles that mimic chylomicrons bias toward lacteal entry, and long-chain fatty acid components enhance this effect. For insulin, where portal-first exposure is desirable, hybrid strategies may route a fraction to the portal vein by targeting enterocyte transporters that drain into the portal circulation, or by designing prodrugs that are cleaved in the portal bed[35].

Protection from proteolysis is crucial. Incorporating protease inhibitors into the nanocarrier microenvironment, using dense hydrogen-bond networks, or burying peptides within hydrophobic cores reduces enzymatic access. pH-responsive cores that condense at intestinal pH further sequester payload until uptake. Once inside enterocytes or M cells, endosomal escape is less important for peptides destined for extracellular receptors, but avoiding lysosomal degradation may still increase yield; ionizable lipids and membrane-disruptive peptides can assist vesicular trafficking[36, 37].

Clinical translation hinges on meaningful bioavailability and low variability. Even single-digit absolute bioavailability may be clinically impactful for potent incretins with long half-lives, provided variability is controlled. Food effects, concomitant medications, and disease-related changes in motility can all modulate absorption; therefore, designs that are buffered against pH and transit variability are preferred[38]. Safety

concerns unique to the gut include chronic low-level permeability changes, microbiome perturbation, and local inflammation; long-term studies should monitor these domains along with systemic immunogenicity. With careful engineering, oral nanocarriers can convert fragile peptides into practical medicines that integrate seamlessly into daily routines.

5. Smart and Stimuli-Responsive Platforms for Glucose-Responsive Insulin

Glucose-responsive systems aim to emulate pancreatic β-cell function by coupling sensing with actuation. Enzymatic platforms use glucose oxidase (GOx) to convert glucose to gluconic acid and hydrogen peroxide, lowering local pH and increasing oxidative potential[39–41]. Nanocarriers embedded with GOx exploit these shifts to trigger insulin release via pH-labile linkers, swelling of acid-sensitive matrices, or oxidative cleavage of thioether or boronate bonds. To mitigate oxygen dependence and peroxide toxicity, catalase or peroxidase mimetics can be co-encapsulated, and oxygen-generating additives can stabilize performance at low tissue oxygen.

Boronic acid–based systems use reversible binding of cis-diols on glucose to phenylboronic acid moieties. At high glucose, competitive binding disrupts cross-links, opening the matrix and liberating insulin[42–44]. These materials operate without enzymes, simplifying stability and sterilization, though careful tuning is needed to maintain specificity and avoid interference from other diols. Lectin-based systems leverage glucose-binding proteins such as ConA to modulate release, but immunogenicity and protein leaching necessitate immobilization strategies and rigorous biocompatibility testing.

Kinetics define clinical utility. Systems must respond within minutes to hyperglycemia yet reduce output as glucose normalizes to minimize hypoglycemia. This requires thin diffusion barriers, high surface area, and finely tuned cross-link density[45]. Incorporating nanoparticles into microneedle patches or subcutaneous hydrogels increases interface with interstitial fluid, accelerating response. For prandial control, layered architectures can produce a rapid initial response followed by sustained basal release, while for basal insulin, damped responsiveness may be preferable to avoid nocturnal hypoglycemia[45].

Reliability over weeks is essential. Enzyme activity drifts, fouling by proteins, and fibrotic encapsulation can blunt responsiveness. Antifouling coatings, zwitterionic brushes, and immune-silent chemistries reduce biofouling, and periodic "reset" mechanisms, thermal or ultrasound-triggered, can restore permeability. Manufacturing considerations include preserving enzyme activity during lyophilization, ensuring batch-to-batch sensor calibration, and establishing in vitro assays that predict in vivo set points using CGM-correlated metrics. Ultimately, glucose-responsive nanocarriers are judged by CGM outcomes: increased time in range, reduced time below range, and attenuated glycemic variability without increasing burden. If they can deliver these outcomes with weekly or monthly maintenance and minimal alarms or user interventions, they offer a compelling alternative or complement to pump-based closed-loop systems.

6. Extra-Subcutaneous Routes and Long-Acting Depots: Pulmonary, Transdermal, and Intraperitoneal Approaches

Pulmonary delivery takes advantage of the vast absorptive surface and thin alveolar barrier. Nanocarrier aerosols can protect peptides during nebulization and enhance epithelial uptake via surfactant-mimetic lipids[46]. Particle aerodynamic diameter must balance deep-lung deposition with exhalation risk; carrier matrices that deaggregate upon inhalation improve uniformity. Safety evaluations must exclude bronchospasm, alveolar macrophage overload, and chronic inflammation, especially with repeated dosing. For incretins with long half-lives, intermittent inhalation could provide rapid onset without injections, whereas insulin inhalation aims for prandial spikes; nanocarriers may reduce dose and variability compared with plain powders[46].

Transdermal routes using microneedles bypass the stratum corneum while minimizing pain. Arrays that dissolve or swell can deposit nanoparticles into the dermis where rich microvasculature supports uptake[47]. Incorporating glucose-responsive chemistries enables closed-loop–like control at the skin interface, and patch platforms integrate naturally with CGM wearables. Formulation viscosity, needle strength, and skin tolerability drive user experience and adherence. For long-acting incretins, in situ–forming depots composed of biodegradable polymers can deliver steady exposure for weeks; encapsulated nanoparticles within these depots further smooth release and protect cargo from hydrolysis[47].

Intraperitoneal delivery, already used in implantable insulin pumps, provides rapid absorption and a portal-leaning gradient. Nanocarriers administered intraperitoneally can be tuned for peritoneal retention or for rapid transit to the portal circulation, potentially offering a practical compromise between physiologic targeting and invasiveness[48]. Safety focuses on peritoneal irritation, adhesions, and infection risk; biolubricious coatings and sterile, low-endotoxin manufacturing are critical.

Across routes, device–drug compatibility shapes feasibility. Inhalers, patches, and pens must deliver consistent doses of nanoparticle suspensions without clogging or shear-induced degradation. Real-world factors like temperature excursions, vibration during shipping, patient handling, stress formulations beyond laboratory conditions[47]. Human factors engineering should inform device design, and stability programs must include device dwell-time testing. Importantly, alternative routes should simplify, not complicate, daily life; monthly clinic-administered depots or weekly at-home patches may be more acceptable than daily manipulations for many patients.

These extra-subcutaneous and long-acting strategies broaden the palette for individualized therapy. By matching route and kinetics to patient preferences and physiology, clinicians can deploy peptide hormones more effectively with fewer side effects and better adherence.

7. Translation, Safety, and Clinical Trial Design for Hormone-Loaded Nanocarriers

Clinical translation begins with establishing equivalence or superiority on outcomes that matter: glycemic control, hypoglycemia risk, weight, and tolerability. Phase 1 studies should characterize pharmacokinetics and pharmacodynamics with intensive sampling and CGM, comparing nanocarrier formulations to reference products under standardized meal challenges[49]. For liver-targeted insulin, surrogate measures of portal exposure, hepatic glucose production via tracer studies, can provide mechanistic validation. For incretin depots, standardized nausea assessments and gastric emptying tests help relate exposure profiles to tolerability.

Safety oversight must anticipate nanomedicine-specific risks: complement activation, anti-PEG or anti-polymer antibodies, particle accumulation in reticuloendothelial organs, and local tissue reactions at administration sites[50]. Re-dosing studies should track immunogenicity over months, and device compatibility with CGM and injection hardware should be verified. Manufacturing under GMP requires tight control of particle attributes and release kinetics; stability-indicating assays must monitor peptide integrity, oxidation, and aggregation. For oral products, bioequivalence across fed and fasted states and minimal drug–drug interactions are essential[50].

Trial design should reflect intended clinical positioning. For insulin, superiority on time in range with non-inferior hypoglycaemia or non-inferior A1c with reduced hypoglycemia are compelling. For incretins, non-inferior A1c with improved gastrointestinal tolerability or fewer discontinuations would justify adoption[51]. Randomized, active-controlled Phase 2/3 trials should include diverse BMI ranges, gastric motility phenotypes, and varying baseline hypoglycemia risk. Pragmatic features, home CGM data uploads, remote assessments, and patient-reported outcome measures capturing treatment burden increase external validity[52].

Regulatory strategy can leverage precedents for long-acting injectables and oral peptides while addressing unique aspects of targeting and responsiveness. Combination products that co-encapsulate hormones and permeation enhancers or enzymes may require additional toxicology. Environmental and occupational safety around nanoparticle manufacturing should be documented. From an equity perspective, cost and access must be considered early; scalable, solvent-minimizing processes and simple devices support affordability and global reach.

Ultimately, success will be judged in everyday life: fewer injections, more time in range, less nausea, and simpler routines. A translational program that centers these outcomes while rigorously documenting safety and manufacturing reproducibility can bring targeted nanocarriers from concept to clinic for people living with T2D.

CONCLUSIONS

Targeted nanocarriers provide a path to harmonize the pharmacology of insulin and incretin therapies with human physiology and patient preferences. By stabilizing peptides, navigating biological barriers, and directing exposure to desired tissues, nanoparticles can deliver hepatic-first insulin action, smoother incretin kinetics, and even glucose-responsive control that reduces hypoglycemia. Advances in oral, pulmonary, transdermal, and depot formulations expand options beyond daily injections, while smart materials translate glycemic cues into adaptive release. The road to clinical impact passes through meticulous engineering, GMP-ready manufacturing, and trials that prioritize CGM-based outcomes, tolerability, and usability. If these elements align, nanocarrier-enabled hormone delivery can transform T2D management from a regimen of compromises into a more precise, safer, and patient-friendly practice, complementing lifestyle measures and contemporary pharmacotherapy.

REFERENCES

1. Shang, C., Yuan, M., Wang, Y., Wang, Y., Bao, W., Zeng, S., Zhang, D., Liu, P., Sun, L.: Association Between Visceral Obesity and Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Retrospective Study. Diabetes Metab. Syndr. Obes. 17, 2869–2880 (2024). https://doi.org/10.2147/DMSO.S470836
2. Alum, E.U.: Optimizing patient education for sustainable self-management in type 2 diabetes. Discov. Public Health. 22, 44 (2025). https://doi.org/10.1186/s12982-025-00445-5
3. Baliou, S., Apetroaei, M.-M., Hatzidaki, E., Kuzmin, S.V., Tzatzarakis, M.N., Arsene, A.L., Tsatsakis, A., Ioannou, P.: The Interplay Between Obesity and Type 2 Diabetes: Common Pathophysiological Mechanisms Contributing to Telomere Shortening. Life. 15, 873 (2025). https://doi.org/10.3390/life15060873
4. Ejemot-Nwadiaro, R.I., Betiang, P.A., Basajja, M., Uti, D.E.: Obesity and Climate Change: A Two-way Street with Global Health Implications. Obes. Med. 56, 100623 (2025). https://doi.org/10.1016/j.obmed.2025.100623
5. Izah, S.C., Betiang, P.A., Paul-Chima Ugwu, O., Ainebyoona, C., Uti, D.E., Echegu, D.A., Alum, B.N.: The Ketogenic Diet in Obesity Management: Friend or Foe? Cell Biochem. Biophys. (2025). https://doi.org/10.1007/s12013-025-01878-0

6. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., De Campos, O.C., Udeozor, P.A., Nfona, S.O., Lawal, B., Alum, E.U.: Modulation of Lipogenesis by Tetracarpidium conophorum Nuts via SREBP-1/ACCA-1/FASN Inhibition in Monosodium-Glutamate-Induced Obesity in Rats. Nat. Prod. Commun. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035
7. 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
8. Azmi, N.A.N., Elgharbawy, A.A.M.: Advances in Medical Applications: The Quest of Green Nanomaterials. In: Shanker, U., Hussain, C.M., and Rani, M. (eds.) Handbook of Green and Sustainable Nanotechnology: Fundamentals, Developments and Applications. pp. 1889–1909. Springer International Publishing, Cham (2023)
9. Awlqadr, F.H., Majeed, K.R., Altemimi, A.B., Hassan, A.M., Qadir, S.A., Saeed, M.N., Faraj, A.M., Salih, T.H., Abd Al-Manhel, A.J., Najm, M.A.A., Tsakali, E., Van Impe, J.F.M., Abd El-Maksoud, A.A., Abedelmaksoud, T.G.: Nanotechnology-based herbal medicine: Preparation, synthesis, and applications in food and medicine. J. Agric. Food Res. 19, 101661 (2025). https://doi.org/10.1016/j.jafr.2025.101661
10. Ghadami, A., Fathi-karkan, S., Siddiqui, B., Gondal, S.A., Rahdar, A., Garousi, N.A., Kharaba, Z., Ghotekar, S.: Nanotechnology in Imatinib delivery: advancing cancer treatment through innovative nanoparticles. Med. Oncol. 42, 116 (2025). https://doi.org/10.1007/s12032-025-02660-1
11. 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. Obes. Med. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585
12. 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. Nat. Prod. Commun. 20, 1934578X251323393 (2025). https://doi.org/10.1177/1934578X251323393
13. 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
14. Kapalatiya, H., Madav, Y., Tambe, V.S., Wairkar, S.: Enzyme-responsive smart nanocarriers for targeted chemotherapy: an overview. Drug Deliv. Transl. Res. 12, 1293–1305 (2022). https://doi.org/10.1007/s13346-021-01020-6
15. Karnwal, A., Sharma, V., Kumar, G., Jassim, A.Y., Dohroo, A., Sivanesan, I.: Transforming Medicine with Nanobiotechnology: Nanocarriers and Their Biomedical Applications. Pharmaceutics. 16, 1114 (2024). https://doi.org/10.3390/pharmaceutics16091114
16. Hsu, C.-Y., Wang, P.-W., Alalaiwe, A., Lin, Z.-C., Fang, J.-Y.: Use of Lipid Nanocarriers to Improve Oral Delivery of Vitamins. Nutrients. 11, 68 (2019). https://doi.org/10.3390/nu11010068
17. 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
18. Scharf, M., Feriz, K., Yepes, C., Contreras, Á., Lequi, L., Sanhueza, D., Krakauer, M., Márquez, E., Ré, M., Mehta, R.: Consensus statement on standardizing CGM evaluation metrics in Latin America: an expert approach. Diabetol. Metab. Syndr. 17, 291 (2025). https://doi.org/10.1186/s13098-025-01851-0
19. Ehrmann, D., Priesterroth, L., Schmitt, A., Kulzer, B., Hermanns, N.: Associations of Time in Range and Other Continuous Glucose Monitoring–Derived Metrics With Well-Being and Patient-Reported Outcomes: Overview and Trends. Diabetes Spectr. Publ. Am. Diabetes Assoc. 34, 149–155 (2021). https://doi.org/10.2337/ds20-0096
20. Zhu, Q., Chen, Z., Paul, P.K., Lu, Y., Wu, W., Qi, J.: Oral delivery of proteins and peptides: Challenges, status quo and future perspectives. Acta Pharm. Sin. B. 11, 2416–2448 (2021). https://doi.org/10.1016/j.apsb.2021.04.001
21. Rama, B., Ribeiro, A.J.: Role of nanotechnology in the prolonged release of drugs by the subcutaneous route. Expert Opin. Drug Deliv. 20, 559–577 (2023). https://doi.org/10.1080/17425247.2023.2214362
22. Holst, J.J., Gasbjerg, L.S., Rosenkilde, M.M.: The Role of Incretins on Insulin Function and Glucose Homeostasis. Endocrinology. 162, bqab065 (2021). https://doi.org/10.1210/endocr/bqab065
23. Nawaz, A., Fujisaka, S., Kado, T., Jeelani, I., Tobe, K.: Heterogeneity of adipose tissue-resident macrophages-beyond M1/M2 paradigm. Diabetol. Int. 14, 125–133 (2023). https://doi.org/10.1007/s13340-023-00624-2
24. Afzal, O., Altamimi, A.S.A., Nadeem, M.S., Alzarea, S.I., Almalki, W.H., Tariq, A., Mubeen, B., Murtaza, B.N., Iftikhar, S., Riaz, N., Kazmi, I.: Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials. 12, 4494 (2022). https://doi.org/10.3390/nano12244494

25. Al-Thani, A.N., Jan, A.G., Abbas, M., Geetha, M., Sadasivuni, K.K.: Nanoparticles in cancer theragnostic and drug delivery: A comprehensive review. Life Sci. 352, 122899 (2024). https://doi.org/10.1016/j.lfs.2024.122899
26. Alfutaimani, A.S., Alharbi, N.K., S. Alahmari, A., A. Alqabbani, A., Aldayel, A.M.: Exploring the landscape of Lipid Nanoparticles (LNPs): A comprehensive review of LNPs types and biological sources of lipids. Int. J. Pharm. X. 8, 100305 (2024). https://doi.org/10.1016/j.ijpx.2024.100305
27. Bai, X., Smith, Z.L., Wang, Y., Butterworth, S., Tirella, A.: Sustained Drug Release from Smart Nanoparticles in Cancer Therapy: A Comprehensive Review. Micromachines. 13, 1623 (2022). https://doi.org/10.3390/mi13101623
28. Bashir, S., Amn Zia, M., Shoukat, M., Kaleem, I., Bashir, S.: Nanoparticles as a novel key driver for the isolation and detection of circulating tumour cells. Sci. Rep. 14, 22580 (2024). https://doi.org/10.1038/s41598-024-67221-4
29. Bandyopadhyay, K., Singh, S., Chaturvadi, V.K., Singh, A.K., Verma, A.: Recent advances in NIR-II emitting nanomaterials: design and biomedical applications of lanthanide complexes and functionalized mesoporous silica nanoparticles (MSNs). J. Mater. Chem. B. (2025). https://doi.org/10.1039/D5TB00911A
30. M. Ways, T.M., Lau, W.M., Khutoryanskiy, V.V.: Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. Polymers. 10, 267 (2018). https://doi.org/10.3390/polym10030267
31. Yang, J., Cao, Z.: Glucose-responsive insulin release: Analysis of mechanisms, formulations, and evaluation criteria. J. Control. Release Off. J. Control. Release Soc. 263, 231–239 (2017). https://doi.org/10.1016/j.jconrel.2017.01.043
32. Jacob, S., Kather, F.S., Boddu, S.H.S., Attimarad, M., Nair, A.B.: Nanosuspension Innovations: Expanding Horizons in Drug Delivery Techniques. Pharmaceutics. 17, 136 (2025). https://doi.org/10.3390/pharmaceutics17010136
33. Din, F. ud, Aman, W., Ullah, I., Qureshi, O.S., Mustapha, O., Shafique, S., Zeb, A.: Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int. J. Nanomedicine. 12, 7291–7309 (2017). https://doi.org/10.2147/IJN.S146315
34. Jalili, C., Kiani, A., Gholami, M., Bahrehmand, F., Fakhri, S., Kakehbaraei, S., Kakebaraei, S.: Brain targeting based nanocarriers loaded with resveratrol in Alzheimer's disease: A review. IET Nanobiotechnol. 17, 154–170 (2023). https://doi.org/10.1049/nbt2.12127
35. Horowitz, A., Chanez-Paredes, S.D., Haest, X., Turner, J.R.: Paracellular permeability and tight junction regulation in gut health and disease. Nat. Rev. Gastroenterol. Hepatol. 1–16 (2023). https://doi.org/10.1038/s41575-023-00766-3
36. Lucana, M.C., Arruga, Y., Petrachi, E., Roig, A., Lucchi, R., Oller-Salvia, B.: Protease-Resistant Peptides for Targeting and Intracellular Delivery of Therapeutics. Pharmaceutics. 13, 2065 (2021). https://doi.org/10.3390/pharmaceutics13122065
37. Li, Y., Zhang, C., Li, G., Deng, G., Zhang, H., Sun, Y., An, F.: Protease-triggered bioresponsive drug delivery for the targeted theranostics of malignancy. Acta Pharm. Sin. B. 11, 2220–2242 (2021). https://doi.org/10.1016/j.apsb.2021.01.017
38. Deacon, C.F., Ahrén, B.: Physiology of Incretins in Health and Disease. Rev. Diabet. Stud. RDS. 8, 293–306 (2011). https://doi.org/10.1900/RDS.2011.8.293
39. Ashrafizadeh, M., Delfi, M., Zarrabi, A., Bigham, A., Sharifi, E., Rabiee, N., Paiva-Santos, A.C., Kumar, A.P., Tan, S.C., Hushmandi, K., Ren, J., Zare, E.N., Makvandi, P.: Stimuli-responsive liposomal nanoformulations in cancer therapy: Pre-clinical & clinical approaches. J. Controlled Release. 351, 50–80 (2022). https://doi.org/10.1016/j.jconrel.2022.08.001
40. Du, J., Lane, L.A., Nie, S.: Stimuli-Responsive Nanoparticles for Targeting the Tumor Microenvironment. J. Control. Release Off. J. Control. Release Soc. 219, 205–214 (2015). https://doi.org/10.1016/j.jconrel.2015.08.050
41. Khalil, A.K.A., Teow, Y.H., Takriff, M.S., Ahmad, A.L., Atieh, M.A.: Recent developments in stimuli-responsive polymer for emerging applications: A review. Results Eng. 25, 103900 (2025). https://doi.org/10.1016/j.rineng.2024.103900
42. 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. J. Drug Deliv. Sci. Technol. 112, 107238 (2025). https://doi.org/10.1016/j.jddst.2025.107238
43. Wang, T., Wu, C., Hu, Y., Zhang, Y., Ma, J.: Stimuli-responsive nanocarrier delivery systems for Pt-based antitumor complexes: a review. (2023). https://doi.org/10.1039/D3RA00866E
44. Wang, T., Liu, Y., Wu, Q., Lou, B., Liu, Z.: DNA nanostructures for stimuli-responsive drug delivery. Smart Mater. Med. 3, 66–84 (2022). https://doi.org/10.1016/j.smaim.2021.12.003

45. Hahn, R.G., Svensson, R., Zdolsek, J.H.: Kinetics of crystalloid fluid in hyperglycemia; an open-label exploratory clinical trial. Acta Anaesthesiol. Scand. 64, 1177–1186 (2020). https://doi.org/10.1111/aas.13614
46. Radiom, M., Sarkis, M., Brookes, O., Oikonomou, E.K., Baeza-Squiban, A., Berret, J.-F.: Pulmonary surfactant inhibition of nanoparticle uptake by alveolar epithelial cells. Sci. Rep. 10, 19436 (2020). https://doi.org/10.1038/s41598-020-76332-7
47. Guillot, A.J., Cordeiro, A.S., Donnelly, R.F., Montesinos, M.C., Garrigues, T.M., Melero, A.: Microneedle-Based Delivery: An Overview of Current Applications and Trends. Pharmaceutics. 12, 569 (2020). https://doi.org/10.3390/pharmaceutics12060569
48. 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. Discov. Nano. 20, 70 (2025). https://doi.org/10.1186/s11671-025-04248-0
49. Ono, R., Furihata, K., Ichikawa, Y., Nakazuru, Y., Bergman, A., Gorman, D.N., Saxena, A.R.: A phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of danuglipron (PF-06882961), an oral small-molecule glucagon-like peptide-1 receptor agonist, in Japanese adults with type 2 diabetes mellitus. Diabetes Obes. Metab. 25, 805–814 (2023). https://doi.org/10.1111/dom.14928
50. Gabizon, A., Szebeni, J.: Complement Activation: A Potential Threat on the Safety of Poly(ethylene glycol)-Coated Nanomedicines. ACS Nano. 14, 7682–7688 (2020). https://doi.org/10.1021/acsnano.0c03648
51. Zaccardi, F., Kloecker, D.E., Khunti, K., Davies, M.J.: Non-inferiority and clinical superiority of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors: Systematic analysis of cardiorenal outcome trials in type 2 diabetes. Diabetes Obes. Metab. 24, 1598–1606 (2022). https://doi.org/10.1111/dom.14735
52. Lu, J., Chen, D., Lin, B., Liu, Z., Yang, Y., He, L., Yan, J., Yang, D., Xu, W.: A CGM-Based model for predicting hypoglycemia in type 2 diabetes patients with TIR in target. Diabetol. Metab. Syndr. 17, 169 (2025). https://doi.org/10.1186/s13098-025-01713-9

CITE AS: Mugisha Emmanuel K. (2026). Targeted Nanocarriers for Insulin and Incretin Delivery: Overcoming Barriers in Type 2 Diabetes Management. Research Output Journal of Biological and Applied Science 6(1):11-18. https://doi.org/10.59298/ROJBAS/2026/611118