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Nanoparticle-Based Insulin Delivery Systems: Overcoming Barriers in Obesity-Associated Diabetes

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ABSTRACT

Obesity profoundly alters insulin pharmacokinetics and pharmacodynamics through expanded and inflamed adipose depots, altered subcutaneous tissue architecture, and systemic low-grade inflammation, all of which complicate insulin replacement therapy. Nanoparticle (NP)-based delivery systems offer multiple tools to address these barriers: protection of insulin from degradation, controlled and targeted release, glucose-responsive dosing, and alternative non-injectable routes (oral, inhaled, transdermal). This review summarizes how obesity changes insulin absorption and action, surveys NP platforms (lipid, polymeric, inorganic, hybrid) and administration routes, assesses glucose-responsive and adipose-targeting strategies, and examines preclinical and clinical progress. We highlight translational challenges safety, immunogenicity, scale-up, and regulatory pathways, and propose a roadmap for development that prioritizes patient acceptability, rigorous obesity-relevant models, and biomarker-driven clinical trials. Nanoparticle approaches show promise to improve glycaemic control and adherence in people with obesity-associated diabetes, but success will require coordinated advances in design, testing in obesity-specific physiologies, and early engagement with regulators.

Keywords: insulin delivery, nanoparticles, obesity, glucose-responsive, oral insulin

INTRODUCTION

Insulin replacement remains the cornerstone therapy for type 1 diabetes (T1D) and for many patients with insulin-requiring type 2 diabetes (T2D)[1, 2]. Its introduction transformed diabetes from a fatal disease to a manageable chronic condition, with tight glycemic control significantly reducing long-term complications such as retinopathy, nephropathy, neuropathy, and cardiovascular events. Despite these advances, effective insulin therapy faces numerous challenges, particularly in the context of the rising global prevalence of obesity[3]. Obesity, increasingly common in individuals with T2D and present in a growing subset of T1D patients, introduces both anatomical and physiological barriers that can profoundly alter insulin absorption, distribution, and action. For instance, increased subcutaneous adipose tissue thickness can slow and erratically distribute insulin, leading to unpredictable peak times and reduced efficacy[4, 5]. Additionally, obesity is associated with chronic low-grade inflammation, altered local lymphatic drainage, and modifications in enzymatic activity within adipose tissue. These changes collectively impair insulin pharmacokinetics and necessitate more intensive dosing regimens to achieve glycemic targets[6, 7].

The requirement for higher or more frequent insulin doses in obese patients can exacerbate treatment complexity, reduce adherence, and increase the risk of hypoglycemic episodes, particularly nocturnal hypoglycemia, which remains a major safety concern[8, 9]. Traditional strategies to optimize insulin delivery in obesity, such as altering injection sites or using concentrated insulin formulations, provide only partial solutions and do not fully address the underlying absorption variability. Consequently, there is a pressing need for advanced delivery systems capable of overcoming these anatomical and physiological hurdles while maintaining physiological insulin kinetics[10].

Nanoparticle (NP) technologies have emerged as a highly promising approach in this context, offering several unique advantages over conventional insulin formulations. Nanoparticles can encapsulate insulin and other peptide cargos, protecting them from enzymatic degradation and premature clearance[10, 11]. This encapsulation can be further engineered for controlled or stimulus-responsive release, allowing insulin to be delivered in a manner that more closely mimics endogenous pancreatic secretion in response to fluctuating glucose levels. Stimuli-responsive systems, for example, leverage glucose-sensitive polymers or enzyme-triggered release mechanisms, enabling "smart" insulin delivery that adjusts dynamically to the patient's glycemic status[12–14].

Beyond pharmacokinetic optimization, nanoparticle platforms also open avenues for non-injectable insulin administration, which could improve patient adherence and quality of life. Oral, inhalable, or transdermal nanoparticle-based systems have demonstrated potential in preclinical studies to facilitate absorption through gastrointestinal, pulmonary, or dermal routes, overcoming the limitations of conventional subcutaneous injection[15]. By targeting insulin delivery to specific tissues or cellular compartments, nanoparticles can also enhance local efficacy, reduce systemic exposure, and potentially mitigate adverse effects associated with high-dose insulin therapy[15–17].

Despite these promising developments, several translational gaps remain. Preclinical successes have yet to fully translate into clinically approved therapies, partly due to challenges in large-scale manufacturing, long-term stability, immunogenicity, and regulatory hurdles[18]. Additionally, understanding nanoparticle behavior in complex human physiology, particularly in the setting of obesity-related tissue alterations, remains incomplete. Critical questions include how nanoparticle size, surface chemistry, and targeting ligands affect biodistribution, uptake, and clearance in obese versus lean individuals, as well as the long-term safety of repeated or chronic administration[19].

This review synthesizes the current state of nanoparticle-based insulin delivery, highlighting both technological advances and remaining barriers. By examining innovations in nanoparticle design, controlled release mechanisms, and alternative administration routes, it frames the critical translational gaps that must be addressed to move these therapies from bench to bedside. Ultimately, nanoparticle-based systems offer a promising strategy to overcome the anatomical and physiological challenges posed by obesity, optimize insulin pharmacokinetics, and improve glycemic control in patients with diabetes.

2. Pathophysiological barriers in obesity that affect insulin therapy

Obesity profoundly alters the structural and functional characteristics of subcutaneous adipose tissue, creating significant challenges for insulin therapy[4, 16, 20]. One prominent feature is increased subcutaneous adipose thickness, which changes the anatomical landscape into which insulin is injected. In individuals with substantial fat accumulation, the distance between the skin surface and the underlying capillary network is greater, altering the diffusion gradient that governs insulin absorption[21–23]. This increased diffusion distance slows the transit of insulin from the depot into the circulation, leading to delayed onset of action and reduced peak concentrations. Additionally, obese adipose tissue often exhibits altered cellular composition, with hypertrophied adipocytes, expanded extracellular matrix, and variable regional perfusion. These structural modifications can blunt insulin uptake into both capillaries and lymphatics, reducing the efficiency and predictability of conventional subcutaneous insulin delivery. As a result, standard injection techniques that are effective in lean individuals may become inconsistent in obese patients, necessitating careful consideration of injection depth, site rotation, and potential use of alternative delivery technologies[24, 25].

Beyond structural changes, chronic low-grade inflammation and disrupted microvascular networks within obese adipose tissue further compromise insulin pharmacokinetics. Obesity-associated adipose depots secrete pro-inflammatory cytokines and chemokines that recruit immune cells and perpetuate tissue inflammation[26, 27]. This inflammatory milieu promotes interstitial fibrosis, endothelial dysfunction, and capillary rarefaction, collectively reducing effective tissue perfusion. Impaired microcirculation hinders the dispersion of insulin from the injection site and limits its access to the capillary endothelium for systemic uptake[28]. Furthermore, the inflammatory environment can alter local enzymatic activity and interstitial fluid dynamics, creating additional barriers to predictable insulin absorption. Together, these factors contribute to heightened variability in insulin action between patients and even within the same patient across different injection sites or over time, complicating glycaemic management and increasing the risk of hypo- or hyperglycaemic episodes[29].

Systemic metabolic alterations in obesity introduce yet another layer of complexity in insulin therapy. Elevated circulating free fatty acids, ectopic lipid accumulation in liver and muscle, and dysregulated adipokine signaling collectively interfere with insulin receptor function and downstream signaling pathways[30]. These metabolic disturbances not only attenuate insulin sensitivity but also influence insulin clearance, modifying both the duration and intensity of exogenously administered insulin. Consequently, standard dosing regimens may become insufficient or unpredictable, requiring frequent titration and careful monitoring[30]. The combination of altered tissue architecture, compromised microcirculation, and systemic metabolic derangements highlights the need for innovative insulin delivery strategies in obesity. Emerging approaches, such as depot-modifying formulations, nanoparticle carriers, and alternative administration routes, aim to normalize absorption kinetics or bypass local tissue limitations, ultimately reducing inter- and intra-patient variability and improving overall glycaemic control in this high-risk population[31–33].

3. Nanoparticle platforms for insulin delivery

Nanoparticles provide modular platforms to stabilize insulin and tune its biodistribution. Major classes:

3.1 Lipid-based NPs (liposomes, solid lipid NPs, LNPs): Lipid-based nanoparticles, including liposomes, solid lipid nanoparticles (SLNs), and lipid nanoparticles (LNPs), provide versatile platforms for insulin delivery[17, 34]. They protect insulin from enzymatic degradation, allowing it to remain active during transit through harsh biological environments such as the gastrointestinal tract or pulmonary mucosa[34]. These carriers can be surface-modified with targeting ligands, mucoadhesive polymers, or stealth coatings to enhance tissue specificity and absorption. LNP technology, greatly advanced through mRNA vaccine development,

allows rapid optimization of size, lipid composition, and encapsulation efficiency, facilitating scalable manufacturing of peptide and protein therapeutics while maintaining stability, bioavailability, and controlled release kinetics[35].

3.2 Polymeric NPs (PLGA, chitosan, alginate, dextran derivatives): Polymeric nanoparticles, made from biodegradable polymers such as PLGA, chitosan, alginate, and dextran derivatives, offer sustained release, protection from enzymatic degradation, and tunable pharmacokinetics[36–38]. Their chemical structures can be modified to enhance mucoadhesion, reduce enzymatic breakdown, or impart glucose-responsive release through functional groups such as phenylboronic acid. Enteric coatings protect insulin from stomach acid, allowing absorption in the small intestine. Polymers also enable stimuli-responsive systems that release insulin in response to pH changes or glucose fluctuations, improving glycemic control[37, 39, 40]. The versatility of polymeric carriers makes them highly adaptable for oral, nasal, or injectable delivery while supporting long-term safety and efficacy studies.

3.3 Inorganic and hybrid NPs (silica, gold hybrids): Inorganic nanoparticles, such as silica, gold, and their hybrid systems, provide robust cores for insulin delivery with precise control over particle size, shape, and stability[41]. These cores can be coated with organic polymers or biocompatible shells to improve safety, circulation time, and responsiveness to biological stimuli. Functionalization allows pH-sensitive or glucose-responsive insulin release, while optical or electronic properties enable integration with biosensing technologies for real-time monitoring of glucose levels[41]. Hybrid inorganic-organic NPs thus combine mechanical stability with functional versatility, supporting controlled release, targeted delivery, and theranostic applications, bridging therapeutic administration with advanced diagnostics in diabetes management.

3.4 Peptide- and protein-based nanocarriers: Peptide- and protein-based nanocarriers utilize self-assembling peptides, albumin, gelatin, or other protein matrices to encapsulate insulin in highly biocompatible systems[42]. These carriers minimize immunogenicity while offering controlled release through enzymatic degradation or stimuli-responsive triggers. Peptide sequences can be designed to improve mucosal adhesion, cellular uptake, or glucose-responsive behavior, enhancing therapeutic precision[43]. Albumin- or gelatin-based nanoparticles provide structural integrity and facilitate systemic circulation, while preserving bioactivity of encapsulated insulin. Systematic reviews highlight their potential for oral, nasal, and injectable delivery but caution that comprehensive long-term safety, immunogenicity, and pharmacokinetic studies remain limited, underscoring the need for further translational research[43].

4. Routes of administration and why they matter in obesity

4.1 Subcutaneous (improved injectable formulations & depot NPs): Nanoparticle-based subcutaneous insulin formulations allow modulation of release kinetics to better match physiological needs. By adjusting particle size, surface chemistry, and excipient composition, rapid-acting insulin can be converted into depot forms that provide extended release, or into faster-absorbing formulations that reduce post-prandial hyperglycemia[44]. Such NP depots protect insulin from local enzymatic degradation and maintain structural stability. However, in obesity, increased subcutaneous adipose thickness and altered tissue composition can modify absorption and depot behavior. Therefore, preclinical testing in obesity-relevant models is crucial to ensure predictable pharmacokinetics and to optimize NP design for effective insulin delivery under these altered anatomical conditions[45].

4.2 Oral delivery: Oral insulin offers the advantage of mimicking physiological portal insulin delivery, improving glycemic control and patient adherence. Nanoparticle systems aim to protect insulin from degradation by gastric acid and pancreatic enzymes, facilitate epithelial transcytosis, and enable controlled release into the portal circulation[46]. Strategies include enteric coatings, enzyme inhibitors, mucoadhesive polymers, and receptor- or ligand-mediated transcytosis. Preclinical studies demonstrate promising bioavailability improvements, while early clinical trials highlight safety and partial efficacy[47]. Nevertheless, challenges remain in achieving consistent absorption, protecting peptide integrity, and scaling production. Translation to routine clinical use requires further optimization of NP design, targeting, and stability under variable gastrointestinal conditions.

4.3 Inhaled delivery: Pulmonary insulin delivery leverages the large alveolar surface area and thin capillary barriers to achieve rapid systemic absorption. Modern inhaled formulations, including Technosphere/Afrezza and novel nanoparticle aerosols, have demonstrated faster post-prandial glucose control compared with subcutaneous injections in certain studies[48]. Nanoparticle engineering allows optimization of particle size, surface properties, and aerosol stability to enhance deep lung deposition and avoid aggregation. Safety remains critical, including avoidance of pulmonary inflammation and long-term tolerance issues. Obesity-associated changes in lung mechanics, airway diameter, and ventilation-perfusion patterns may influence deposition and absorption, emphasizing the need for careful formulation design and evaluation in obese patient populations[49].

4.4 Transdermal and microneedle patches: Transdermal and microneedle-based patches offer minimally invasive insulin delivery with potential for controlled and glucose-responsive release. Nanoparticle-loaded hydrogels, polymer matrices, and phenylboronic acid (PBA)-functionalized systems have demonstrated glucose-triggered insulin release in preclinical studies[50]. By bypassing the subcutaneous tissue, these platforms avoid challenges associated with altered adipose thickness, fibrosis, and local perfusion seen in obesity. Microneedles

can penetrate dermal layers with rich capillary networks, ensuring effective systemic uptake[51]. Additionally, nanocarrier incorporation enhances insulin stability, release kinetics, and responsiveness. While early results are promising, clinical translation requires optimization for dose consistency, patch adhesion, biocompatibility, and long-term safety in diverse patient populations[52].

5. Glucose-responsive ('smart') nanoparticle systems

A core objective in advanced insulin delivery systems is to tightly couple insulin release to ambient glucose concentrations, thereby minimizing the risk of hypoglycemia and reducing the frequency of dosing compared with conventional regimens. Several innovative approaches are being explored to achieve this glucose-responsiveness[53]. One strategy involves enzymatic systems, most commonly using glucose oxidase, which converts glucose into gluconic acid and hydrogen peroxide, triggering local pH or oxidative changes that in turn modulate insulin release. Another approach leverages phenylboronic acid (PBA) or lectin-based chemistries that reversibly bind glucose, enabling insulin release in proportion to extracellular glucose levels. Synthetic nanosugars and polymer-based conformational switches offer an alternative by undergoing structural transformations upon glucose binding, releasing insulin in a controlled, reversible manner[54]. Additionally, hybrid systems are being developed that integrate both sensing and release modules, combining enzymatic, chemical, or mechanical triggers to achieve more precise and tunable insulin delivery. Preclinical studies have demonstrated rapid, reversible, and repeatable glucose-triggered insulin release in vitro and in animal models, highlighting the potential of these technologies. However, significant challenges remain, particularly in scaling these systems for human use, ensuring consistent sensitivity across physiological glucose ranges, maintaining long-term biocompatibility, and preventing immune or inflammatory responses[55]. Overcoming these hurdles is essential for translating glucose-responsive insulin into clinical practice.

6. Addressing obesity-specific delivery challenges with nanoparticle design

Particle size and depot behavior: Smaller particles may diffuse more readily from injection sites in fibrotic adipose; larger depots prolong release designs should consider altered interstitial matrix and lymphatic clearance in obese tissue[56].

Targeting alternatives: For obese patients with impaired subcutaneous uptake, non-subcutaneous routes (oral, inhaled, intradermal microneedles) can be prioritized. For subcutaneous strategies, co-formulation with vasodilatory or matrix-modifying agents (carefully evaluated for safety) may normalize uptake[57].

Inflammation and immunogenicity: Chronic adipose inflammation raises concern for NP clearance and immune recognition; "stealth" coatings (PEGylation, zwitterions, 'self' peptides) and minimal immunostimulatory components should be prioritized.)[58]

7. Safety, toxicity and regulatory considerations

Acute and chronic toxicity: NP constituents (materials, surfactants, stabilizers) must be evaluated for pulmonary, gastrointestinal, dermal, and systemic toxicity in long-term studies. Chronic exposure in daily dosing brings unique immunogenicity and accumulation concerns.

Immunogenicity & complement activation: Surface chemistries can activate complement or trigger anti-carrier antibodies, altering PK and safety profiles. Preclinical immunotoxicology should reflect repeated dosing in obesity-relevant models.

Manufacturing & quality control: Reproducible particle size distribution, encapsulation efficiency, endotoxin control, and sterilization are critical. Regulatory pathways for peptide–nanoparticle combination products require early dialogue with authorities to define comparators and endpoints. Recent regulatory attention to nanomedicines and lessons from LNP vaccines can guide scale-up.)

9. Challenges and knowledge gaps

i. **Obesity-specific models are scarce.** Most preclinical testing uses lean models; obesity alters pharmacology and must be represented in PK/PD and safety studies.
ii. **Long-term safety and biodegradation data.** Chronic daily exposure requires rigorous accumulation and metabolite studies.
iii. **Inter-individual PK variability.** Heterogeneity in adipose distribution and inflammation across patients necessitates stratified clinical trial designs and biomarker end points.
iv. **Patient acceptability & adherence.** Non-injectable options offer greater acceptance, but device complexity and cost can limit uptake. Economic analyses early in development help prioritize viable pathways.
v. **Regulatory clarity for combination devices.** Insulin-NP products are combination biologic-device products; harmonized regulatory guidance would accelerate translation.

10. Future directions and roadmap for translation

Effective development of insulin delivery systems for obesity-associated diabetes requires early integration of obesity-specific physiology into design and testing. Preclinical studies should incorporate obese animal models and human adipose tissue explants to capture the altered pharmacokinetics and tissue interactions characteristic of obesity[59]. Prioritizing glucose-responsive, self-regulated systems is critical, as these can adapt insulin release to ambient glucose levels, thereby reducing hypoglycaemia risk, which is particularly pronounced in obese populations. Incorporating hybrid approaches that synergize nanoparticle depots or transdermal patches

with closed-loop sensing and algorithmic insulin titration may further enhance glycaemic control, offering robust and adaptive solutions[60–62]. Early engagement with regulatory bodies and demonstration of manufacturing at scale are equally essential, with frameworks such as quality by design (QbD) ensuring reproducibility and safety. Lessons from lipid nanoparticle (LNP) and mRNA manufacturing can inform scalable production and facilitate smoother translational pathways.

Clinical trials should reflect these complexities by stratifying participants according to BMI and adipose distribution, ensuring that pharmacokinetic and pharmacodynamic endpoints are assessed with relevant biomarkers, such as insulin appearance in portal versus systemic circulation. Inclusion of patient-reported outcomes evaluating convenience, adherence, and quality of life is essential for holistic assessment. Collectively, these strategies integrating obesity physiology, self-regulated release, hybrid technologies, scalable manufacturing, and innovative clinical trial design will improve the efficacy, safety, and real-world applicability of next-generation insulin delivery systems for patients with obesity-driven diabetes.

CONCLUSION

Nanoparticle-based insulin delivery offers multiple strategies to overcome obstacles imposed by obesity protecting insulin, tuning release kinetics, enabling non-injectable routes, and building glucose-responsive behavior. Translation has accelerated, particularly in inhaled platforms and smart materials, but realizing clinical benefit in obesity-associated diabetes will require a focused program: obesity-aware preclinical models, detailed safety studies for chronic use, early manufacturing demonstrations, and trials designed to address heterogeneity in adipose biology. If these gaps are addressed, NP technologies could meaningfully improve glycaemic control, reduce hypoglycaemia, and increase treatment adherence for people living with obesity-associated diabetes.

REFERENCES

1. Pathak, V., Pathak, N.M., O'Neill, C.L., Guduric-Fuchs, J., Medina, R.J.: Therapies for Type 1 Diabetes: Current Scenario and Future Perspectives. Clinical Medicine Insights. Endocrinology and Diabetes. 12, 1179551419844521 (2019). https://doi.org/10.1177/1179551419844521
2. Timmons, J.G., Littlejohn, L., Boyle, J.G., Petrie, J.R.: Recent developments in adjunct therapies for type 1 diabetes. Expert Opinion on Investigational Drugs. 31, 1311–1320 (2022). https://doi.org/10.1080/13543784.2022.2159806
3. Yang, Y., Zhao, B., Wang, Y., Lan, H., Liu, X., Hu, Y., Cao, P.: Diabetic neuropathy: cutting-edge research and future directions. Signal Transduction and Targeted Therapy. 10, 132 (2025). https://doi.org/10.1038/s41392-025-02175-1
4. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. Int J Mol Sci. 25, 1882 (2024). https://doi.org/10.3390/ijms25031882
5. Alum, E.U., 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. Klein, S., Gastaldelli, A., Yki-Järvinen, H., Scherer, P.E.: Why does obesity cause diabetes? Cell Metabolism. 34, 11–20 (2022). https://doi.org/10.1016/j.cmet.2021.12.012
7. Zatterale, F., Longo, M., Naderi, J., Raciti, G.A., Desiderio, A., Miele, C., Beguinot, F.: Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Frontiers in Physiology. 10, 1607 (2020). https://doi.org/10.3389/fphys.2019.01607
8. Emad-Eldin, M., Balata, G.F., Elshorbagy, E.A., Hamed, M.S., Attia, M.S.: Insulin therapy in type 2 diabetes: Insights into clinical efficacy, patient-reported outcomes, and adherence challenges. World J Diabetes. 15, 828–852 (2024). https://doi.org/10.4239/wjd.v15.i5.828
9. 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
10. Kalra, S., Pathan, F., Kshanti, I.A.M., Bay, N.Q., Nagase, T., Oliveria, T., Bajpai, S.: Optimising Insulin Injection Techniques to Improve Diabetes Outcomes. Diabetes Therapy. 14, 1785 (2023). https://doi.org/10.1007/s13300-023-01460-y
11. Pandya, N., Losben, N., Moore, J.: Optimizing insulin delivery for patients with diabetes. Geriatr Nurs. 39, 138–142 (2018). https://doi.org/10.1016/j.gerinurse.2017.11.007
12. Wang, Z., Wang, J., Kahkoska, A.R., Buse, J.B., Gu, Z.: Developing Insulin Delivery Devices with Glucose-Responsiveness. Trends Pharmacol Sci. 42, 31–44 (2021). https://doi.org/10.1016/j.tips.2020.11.002
13. Balasubramaniyam, S., Rathinam, T., Srinivasan, M., Jayarani, S.: Nanocarrier-based insulin delivery: A leap towards a needle-free future. Nano TransMed. 4, 100093 (2025). https://doi.org/10.1016/j.ntm.2025.100093
14. 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
15. Romero-Carmona, C.E., Chávez-Corona, J.I., Lima, E., Cortés, H., Quintanar-Guerrero, D., Bernad-Bernad, M.J., Ramos-Martínez, I., Peña-Corona, S.I., Sharifi-Rad, J., Leyva-Gómez, G.: Nanoparticle and microparticle-based systems for enhanced oral insulin delivery: A systematic review and meta-analysis. J Nanobiotechnol. 22, 802 (2024). https://doi.org/10.1186/s12951-024-03045-8
16. 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
17. Mehta, M., Bui, T.A., Yang, X., Aksoy, Y., Goldys, E.M., Deng, W.: Lipid-Based Nanoparticles for Drug/Gene Delivery: An Overview of the Production Techniques and Difficulties Encountered in Their Industrial Development. ACS Mater. Au. 3, 600–619 (2023). https://doi.org/10.1021/acsmaterialsau.3c00032
18. Liang, Y., Wei, S., Zhang, A.: Bioengineered tracheal graft with enhanced vascularization and mechanical stability for functional airway reconstruction. Regen Ther. 29, 364–380 (2025). https://doi.org/10.1016/j.reth.2025.03.016
19. Zhou, T., Yuan, Z., Weng, J., Pei, D., Du, X., He, C., Lai, P.: Challenges and advances in clinical applications of mesenchymal stromal cells. Journal of Hematology & Oncology. 14, 24 (2021). https://doi.org/10.1186/s13045-021-01037-x
20. Akter, R., Awais, M., Boopathi, V., Ahn, J.C., Yang, D.C., Kang, S.C., Yang, D.U., Jung, S.-K.: Inversion of the Warburg Effect: Unraveling the Metabolic Nexus between Obesity and Cancer. ACS Pharmacology & Translational Science. 7, 560 (2024). https://doi.org/10.1021/acsptsci.3c00301
21. Balan, A.I., Halaţiu, V.B., Scridon, A.: Oxidative Stress, Inflammation, and Mitochondrial Dysfunction: A Link between Obesity and Atrial Fibrillation. Antioxidants (Basel). 13, 117 (2024). https://doi.org/10.3390/antiox13010117
22. Barber, T.M., Kyrou, I., Randeva, H.S., Weickert, M.O.: Mechanisms of Insulin Resistance at the Crossroad of Obesity with Associated Metabolic Abnormalities and Cognitive Dysfunction. Int J Mol Sci. 22, 546 (2021). https://doi.org/10.3390/ijms22020546
23. Bougaret, L., Delort, L., Billard, H., Huede, C.L., Boby, C., Foye, A.D. la, Rossary, A., Mojallal, A., Damour, O., Auxenfans, C., Vasson, M.P., Caldefie-Chezet, F.: Adipocyte/breast cancer cell crosstalk in obesity interferes with the anti-proliferative efficacy of tamoxifen. PLOS ONE. 13, e0191571 (2018). https://doi.org/10.1371/journal.pone.0191571
24. Gradel, A.K.J., Porsgaard, T., Lykkesfeldt, J., Seested, T., Gram-Nielsen, S., Kristensen, N.R., Refsgaard, H.H.F.: Factors Affecting the Absorption of Subcutaneously Administered Insulin: Effect on Variability. J Diabetes Res. 2018, 1205121 (2018). https://doi.org/10.1155/2018/1205121
25. Pitt, J.P., McCarthy, O.M., Hoeg-Jensen, T., Wellman, B.M., Bracken, R.M.: Factors Influencing Insulin Absorption Around Exercise in Type 1 Diabetes. Front. Endocrinol. 11, (2020). https://doi.org/10.3389/fendo.2020.573275
26. Kawai, T., Autieri, M.V., Scalia, R.: Adipose tissue inflammation and metabolic dysfunction in obesity. Am J Physiol Cell Physiol. 320, C375–C391 (2021). https://doi.org/10.1152/ajpcell.00379.2020
27. 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
28. Mauvais-Jarvis, F.: Novel Link Between Inflammation, Endothelial Dysfunction, and Muscle Insulin Resistance. Diabetes. 62, 688–690 (2013). https://doi.org/10.2337/db12-1434
29. Apostolopoulou, M., Lambadiari, V., Roden, M., Dimitriadis, G.D.: Insulin Resistance in Type 1 Diabetes: Pathophysiological, Clinical, and Therapeutic Relevance. Endocr Rev. 46, 317–348 (2025). https://doi.org/10.1210/endrev/bnae032
30. Cao, X., Wang, N., Yang, M., Zhang, C.: Lipid Accumulation and Insulin Resistance: Bridging Metabolic Dysfunction-Associated Fatty Liver Disease and Chronic Kidney Disease. International Journal of Molecular Sciences. 26, 6962 (2025). https://doi.org/10.3390/ijms26146962
31. Ajnai, G., Cheng, C.-C., Kan, T.-C., Lu, J.-W., Rahayu, S., Chiu, A., Chang, J.: Improving Tirapazamine (TPZ) to Target and Eradicate Hypoxia Tumors by Gold Nanoparticle Carriers. Pharmaceutics. 14, 847 (2022). https://doi.org/10.3390/pharmaceutics14040847
32. Aslam, R., Tiwari, V., Upadhyay, P., Tiwari, A.: REVOLUTIONIZING THERAPEUTIC DELIVERY: DIOSGENIN-LOADED SOLID LIPID NANOPARTICLES UNLEASH ADVANCED CARRIERS. International Journal of Applied Pharmaceutics. 124–133 (2024). https://doi.org/10.22159/ijap.2024v16i1.49306
33. Sun, H., Li, Y., Xue, M., Feng, D.: Tumor Microenvironment-Responsive Nanoparticles: Promising Cancer PTT Carriers. Int J Nanomedicine. 20, 7987–8001 (2025). https://doi.org/10.2147/IJN.S526497

34. Gabel, M., Knauss, A., Fischer, D., Neurath, M.F., Weigmann, B.: Surface Design Options in Polymer- and Lipid-Based siRNA Nanoparticles Using Antibodies. Int J Mol Sci. 23, 13929 (2022). https://doi.org/10.3390/ijms232213929
35. Mehta, M., Bui, T.A., Yang, X., Aksoy, Y., Goldys, E.M., Deng, W.: Lipid-Based Nanoparticles for Drug/Gene Delivery: An Overview of the Production Techniques and Difficulties Encountered in Their Industrial Development. ACS Mater Au. 3, 600–619 (2023). https://doi.org/10.1021/acsmaterialsau.3c00032
36. Austria, E., Bilek, M., Varamini, P., Akhavan, B.: Breaking biological barriers: Engineering polymeric nanoparticles for cancer therapy. Nano Today. 60, 102552 (2025). https://doi.org/10.1016/j.nantod.2024.102552
37. Chis, A.A., Arseniu, A.M., Morgovan, C., Dobrea, C.M., Frum, A., Juncan, A.M., Butuca, A., Ghibu, S., Gligor, F.G., Rus, L.L.: Biopolymeric Prodrug Systems as Potential Antineoplastic Therapy. Pharmaceutics. 14, 1773 (2022). https://doi.org/10.3390/pharmaceutics14091773
38. George Joy, J., Sharma, G., Kim, J.-C.: Tailoring polymeric nanocarriers for hypoxia-specific drug release: Insights into design and applications in clinics. Chemical Engineering Journal. 496, 153978 (2024). https://doi.org/10.1016/j.cej.2024.153978
39. Yu, Z., Shen, X., Yu, H., Tu, H., Chittasupho, C., Zhao, Y.: Smart Polymeric Nanoparticles in Cancer Immunotherapy. Pharmaceutics. 15, 775 (2023). https://doi.org/10.3390/pharmaceutics15030775
40. Zhang, W., Mehta, A., Tong, Z., Esser, L., Voelcker, N.H.: Development of Polymeric Nanoparticles for Blood–Brain Barrier Transfer—Strategies and Challenges. Advanced Science. 8, 2003937 (2021). https://doi.org/10.1002/advs.202003937
41. 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
42. Kianfar, E.: Protein nanoparticles in drug delivery: animal protein, plant proteins and protein cages, albumin nanoparticles. J Nanobiotechnology. 19, 159 (2021). https://doi.org/10.1186/s12951-021-00896-3
43. Zhang, X., Li, X., Zhao, Y., Zheng, Q., Wu, Q., Yu, Y.: Nanocarrier system: An emerging strategy for bioactive peptide delivery. Front. Nutr. 9, (2022). https://doi.org/10.3389/fnut.2022.1050647
44. 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. 17, 945 (2024). https://doi.org/10.3390/ph17070945
45. Magill, E., Demartis, S., Gavini, E., Permana, A.D., Thakur, R.R.S., Adrianto, M.F., Waite, D., Glover, K., Picco, C.J., Korelidou, A., Detamornrat, U., Vora, L.K., Li, L., Anjani, Q.K., Donnelly, R.F., Domínguez-Robles, J., Larrañeta, E.: Solid implantable devices for sustained drug delivery. Advanced Drug Delivery Reviews. 199, 114950 (2023). https://doi.org/10.1016/j.addr.2023.114950
46. Zhang, E., Zhu, H., Song, B., Shi, Y., Cao, Z.: Recent Advances in Oral Insulin Delivery Technologies. J Control Release. 366, 221–230 (2024). https://doi.org/10.1016/j.jconrel.2023.12.045
47. Zhou, S., Chen, Z., Li, X., Yue, F., Ma, L., Zhao, S., Wang, F., Luo, J.: Metformin-based internally charged nanoparticles for oral insulin delivery with injection-matched efficacy. Materials & Design. 257, 114484 (2025). https://doi.org/10.1016/j.matdes.2025.114484
48. Cunningham, S.M., Tanner, D.A.: A Review: The Prospect of Inhaled Insulin Therapy via Vibrating Mesh Technology to Treat Diabetes. International Journal of Environmental Research and Public Health. 17, 5795 (2020). https://doi.org/10.3390/ijerph17165795
49. Cojocaru, E., Petriş, O.R., Cojocaru, C.: Nanoparticle-Based Drug Delivery Systems in Inhaled Therapy: Improving Respiratory Medicine. Pharmaceuticals (Basel). 17, 1059 (2024). https://doi.org/10.3390/ph17081059
50. 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
51. Martínez-Navarrete, M., Pérez-López, A., Guillot, A.J., Cordeiro, A.S., Melero, A., Aparicio-Blanco, J.: Latest advances in glucose-responsive microneedle-based systems for transdermal insulin delivery. International Journal of Biological Macromolecules. 263, 130301 (2024). https://doi.org/10.1016/j.ijbiomac.2024.130301
52. Kim, M., Shin, M., Zhao, Y., Ghosh, M., Son, Y.-O.: Transformative Impact of Nanocarrier-Mediated Drug Delivery: Overcoming Biological Barriers and Expanding Therapeutic Horizons. Small Science. 4, 2400280 (2024). https://doi.org/10.1002/smsc.202400280
53. Donnor, T., Sarkar, S.: Insulin- Pharmacology, Therapeutic Regimens and Principles of Intensive Insulin Therapy. 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)

54. Low, C.Y., Gan, W.L., Lai, S.J., Tam, R.S.-M., Tan, J.F., Dietl, S., Chuah, L.H., Voelcker, N., Bakhtiar, A.: Critical updates on oral insulin drug delivery systems for type 2 diabetes mellitus. Journal of Nanobiotechnology. 23, 16 (2025). https://doi.org/10.1186/s12951-024-03062-7
55. 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
56. DeBari, M.K., Abbott, R.D.: Adipose Tissue Fibrosis: Mechanisms, Models, and Importance. Int J Mol Sci. 21, 6030 (2020). https://doi.org/10.3390/ijms21176030
57. Li, Z., Fang, X., Yu, D.: Transdermal Drug Delivery Systems and Their Use in Obesity Treatment. Int J Mol Sci. 22, 12754 (2021). https://doi.org/10.3390/ijms222312754
58. Lan, X., Johnston, E., Ning, T., Chen, G., Haglund, L., Li, J.: Immunomodulatory bioadhesive technologies. Biomaterials. 321, 123274 (2025). https://doi.org/10.1016/j.biomaterials.2025.123274
59. Luca, T., Pezzino, S., Puleo, S., Castorina, S.: Lesson on obesity and anatomy of adipose tissue: new models of study in the era of clinical and translational research. J Transl Med. 22, 764 (2024). https://doi.org/10.1186/s12967-024-05547-3
60. Chandrasekaran, P., Weiskirchen, R.: The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. International Journal of Molecular Sciences. 25, 1882 (2024). https://doi.org/10.3390/ijms25031882
61. Umoru, G.U., Atangwho, I.J., David-Oku, E., Uti, D.E., Agwupuye, E.I., Obeten, U.N., Maitra, S., Subramaniyan, V., Wong, L.S., Aljarba, N.H., Kumarasamy, V.: Tetracarpidium conophorum nuts (African walnuts) up-regulated adiponectin and PPAR-γ expressions with reciprocal suppression of TNF-α gene in obesity. J Cell Mol Med. 28, e70086 (2024). https://doi.org/10.1111/jcmm.70086
62. 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. Natural Product Communications. 20, 1934578X251344035 (2025). https://doi.org/10.1177/1934578X251344035

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