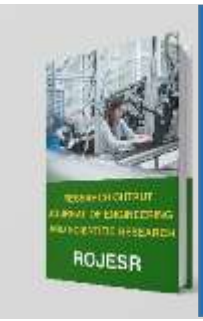

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Smart Nanocarriers for Targeted Delivery of Anti-Obesity Agents: Precision Medicine Approaches to Metabolic Regulation

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ABSTRACT

Obesity is a multifactorial, relapsing disease driven by complex interactions between genetics, environment, and behavior. Conventional systemic pharmacotherapy often fails to provide durable weight loss and is limited by off-target toxicity in the cardiovascular, hepatic, and central nervous systems. Precision delivery of anti-obesity agents to specific tissues and cell populations offers a rational strategy to increase efficacy while reducing adverse effects. Smart nanocarriers engineered to sense local microenvironmental cues, respond to external stimuli, and recognize molecular markers—are emerging as powerful tools to achieve this goal. This review outlines the pathophysiological rationale for targeted delivery in obesity, design principles of smart nanocarriers, and organ-specific targeting strategies for adipose tissue, liver, gut, and CNS. We discuss stimuli-responsive and logic-gated systems, nano-enabled delivery of small molecules, peptides, biologics, and nucleic acids, as well as integration with diagnostics for precision medicine. Finally, we address safety, regulatory, and implementation challenges that must be overcome before these technologies can be deployed in routine metabolic care.

Keywords: Obesity; Smart nanocarriers; Targeted drug delivery; Precision medicine; Metabolic regulation

INTRODUCTION

Obesity is not simply an excess of body weight but a chronic, relapsing disease characterized by dysregulated energy balance, adipose tissue dysfunction, ectopic fat deposition, and altered neuroendocrine signaling[1–3]. Adipose tissue expands through hypertrophy and hyperplasia, accompanied by hypoxia, low-grade inflammation, and remodeling of vasculature and extracellular matrix. Parallel changes occur in liver (steatosis, insulin resistance), skeletal muscle (impaired glucose uptake), pancreas (β-cell stress), and brain (altered reward and satiety circuits)[4–6].

Pharmacologic management of obesity aims to reduce energy intake, increase energy expenditure, or modulate nutrient absorption. Current agents include centrally acting appetite suppressants (e.g., monoamine modulators, GLP-1 receptor agonists), peripherally acting lipase inhibitors, and incretin-based drugs that influence glucose and weight[1, 7]. While these therapies can produce clinically significant weight loss in many patients, their performance is constrained by systemic exposure. Centrally acting drugs may cause nausea, mood changes, or cardiovascular events; peripherally acting agents may affect liver or gastrointestinal function; and long-term safety data remain incomplete for some new modalities[8].

Off-target effects are particularly problematic because obesity treatment is often chronic and administered to individuals who may already carry elevated cardiometabolic risk[9]. The therapeutic window is therefore narrow: sufficient pharmacologic pressure must be applied to overcome homeostatic defense of body weight, but not so much that adverse events become unacceptable[9]. Moreover, obesity is heterogeneous. Some individuals exhibit predominant visceral adiposity with severe insulin resistance; others have more subcutaneous fat and milder metabolic disturbances. Genetic variants, microbiome composition, and behavioral factors further

diversify responses to any given drug. A "one-dose-fits-all" systemic regimen is poorly aligned with this complexity[9, 10].

Targeted drug delivery seeks to resolve part of this dilemma by concentrating therapies where they are needed while sparing other tissues. For obesity and metabolic disease, key target sites include:

i. **White and brown adipose depots** – to modulate lipolysis, lipogenesis, inflammation, and thermogenesis[11, 12].
ii. **Liver** – to correct steatosis, improve insulin sensitivity, and regulate VLDL production.
iii. **Gut** – to modulate nutrient absorption, enteroendocrine signaling, and microbiota composition.
iv. **Pancreas** – to support β-cell function and survival.
v. **Hypothalamus and reward circuits** – to recalibrate appetite and hedonic feeding.

Conventional targeting approaches like prodrugs, depot injections, and local delivery have limitations in spatial specificity and controllability. Nanotechnology, in contrast, allows drugs to be packaged within carriers whose size, surface chemistry, and responsiveness can be precisely tuned. These smart nanocarriers can[13, 14]:

Exploit pathophysiological features of obese tissues, such as leaky vasculature, acidic or oxidative microenvironments, and altered enzyme expression, to accumulate preferentially and release cargo locally.

Engage specific molecular markers, e.g., receptors or adhesion molecules on adipocytes, hepatic cells, or endothelial cells, through conjugated targeting ligands.

Respond to exogenous stimuli light, ultrasound, and magnetic fields, to trigger on-demand drug release in anatomically defined regions.

Perform logic operations, releasing cargo only when multiple conditions are met (e.g., low pH AND high ROS), thereby improving specificity.

Precision medicine adds another dimension: not only where drugs go, but *to whom* and *how much.* Individual variation in BAT abundance, visceral vs subcutaneous fat distribution, hepatic fat content, or gut microbiota means that optimal targets and doses differ across patients[15]. Smart nanocarriers can potentially be combined with imaging, circulating biomarkers, and genotyping to stratify patients and adapt therapy. For example, an individual with extensive hepatic steatosis but modest visceral adiposity might benefit from liver-targeted nano-formulations of insulin sensitizers, whereas someone with high visceral fat and poor BAT activity may be better suited to adipose-targeted thermogenic agents[15]. Smart nanocarriers also offer opportunities for multimodal intervention. Many anti-obesity effects require simultaneous modulation of several organs and pathways e.g., appetite, gut hormones, adipose inflammation, and liver lipid metabolism. Co-delivery of multiple agents in defined ratios can be facilitated by nanocarrier architectures with different compartments or layers[16]. This might enable, for instance, combined delivery of a low-dose GLP-1 analogue with an adipose-acting anti-inflammatory and a liver-directed PPAR agonist, while maintaining distinct release profiles and minimizing systemic peaks[1, 17].

Altogether, the convergence of obesity pathophysiology, precision medicine, and nanotechnology provides a strong conceptual foundation for smart nano-delivery. The following sections examine how nanocarriers are engineered, targeted, and controlled to translate this concept into practical anti-obesity strategies.

2. Design Principles of Smart Nanocarriers for Metabolic Disease Therapy

Smart nanocarriers are engineered assemblies such as lipid-based, polymeric, inorganic, or hybrid—that encapsulate therapeutic payloads and incorporate design features enabling targeted, responsive behavior. Several core principles guide their development for obesity and metabolic disease[16].

Size and shape critically influence circulation, biodistribution, and tissue penetration. Particles in the 50–200 nm range generally avoid rapid renal clearance while passing through fenestrated or inflamed microvasculature. Spherical particles are easiest to manufacture and characterize, but rod-like or discoidal shapes can exhibit distinct margination and adhesion properties in microvessels, potentially improving accumulation in adipose or hepatic sinusoids[18, 19].

Surface chemistry dictates interactions with plasma proteins and cells. Hydrophilic coatings, especially PEG, reduce opsonization and prolong circulation but may provoke anti-PEG antibodies with repeated dosing[20]. Zwitterionic or biomimetic coatings (e.g., cell membranes) offer alternatives. Functional groups on the surface allow conjugation of targeting ligands, peptides, antibodies, aptamers, or small molecules that recognize receptors overexpressed on adipocytes, hepatocytes, or intestinal cells[20].

Payload compatibility and release kinetics are key constraints. Anti-obesity agents include hydrophobic small molecules, fragile peptides, nucleic acids, and biologics. The carrier matrix must protect the cargo from degradation, maintain its activity, and release it at a therapeutically appropriate rate[21]. Hydrophobic cores (e.g., in polymeric micelles or solid lipid nanoparticles) suit lipophilic drugs, whereas ionizable lipids or cationic polymers are used for RNA complexation. Degradation rates of polymers such as PLGA can be tuned by monomer ratio and molecular weight, providing sustained release over days to weeks[21].

Smart functionality arises from stimuli-responsiveness. Materials can be engineered to change solubility, charge, or structure in response to pH, redox conditions, enzymes, temperature, or external fields. In obesity, mildly acidic and oxidative microenvironments in inflamed adipose or diseased liver can trigger selective release[21, 22]. Enzyme-sensitive linkers, cleaved by lipases or matrix metalloproteinases, further refine spatial specificity.

Externally applied stimuli such as NIR light or ultrasound allow clinicians to control the timing and location of drug release.

Multi-compartment and modular architectures offer versatility. Core–shell nanoparticles, layer-by-layer assemblies, and liposome–polymer hybrids can segregate different cargos or integrate imaging agents alongside drugs[23]. Modular design facilitates swapping of targeting ligands or payloads without re-optimizing the entire system, which is advantageous given the heterogeneity of obesity[23].

Finally, practical considerations manufacturability, scalability, and reproducibility must be embedded from the outset. Formulation methods (microfluidics, nanoprecipitation, self-assembly) should yield narrow size distributions and be amenable to GMP upscaling[24]. Analytical tools must robustly characterize size, polydispersity, zeta potential, drug loading, and release profiles. These design principles underpin the development of smart nanocarriers capable of precise and reliable drug delivery in metabolic disease.

3. Targeting Strategies for Adipose Tissue, Liver, Gut, and CNS

Effective obesity therapy often requires selective engagement of specific organs. Smart nanocarriers exploit anatomical and molecular features unique to each target.

Adipose tissue targeting focuses on both white and brown depots. Passive accumulation can occur via enhanced permeability and retention–like effects in inflamed, hypertrophic adipose tissue[11, 25, 26]. Active targeting uses ligands that bind adipocyte or adipose vasculature markers, such as prohibitin-targeting peptides, integrin-binding motifs (e.g., RGD), or antibodies against endothelial markers upregulated in obese adipose tissue[27]. Hydrophobic modifications that favor partitioning into lipid-rich environments can further enhance adipose localization. For browning and lipolysis modulation, nanocarriers may be injected systemically or locally into specific depots to achieve regional effects.

Liver targeting is particularly important for patients with non-alcoholic fatty liver disease and insulin resistance[28]. The liver's fenestrated sinusoidal endothelium and high expression of asialoglycoprotein receptor (ASGPR) on hepatocytes facilitate targeted delivery. Galactose or N-acetylgalactosamine (GalNAc) ligands on nanoparticles promote hepatocyte uptake, a strategy already used clinically for siRNA therapeutics[28]. Appropriate particle size and charge also exploit natural clearance pathways via Kupffer cells or hepatocytes. Anti-obesity agents delivered to the liver may include PPAR agonists, FGF mimetics, or RNAi against key lipogenic enzymes.

Gut targeting can modulate nutrient sensing, hormone secretion (GLP-1, PYY, GIP), and microbiota composition[29]. Oral nano-formulations must overcome harsh gastric conditions and mucosal barriers. Strategies include pH-responsive coatings that dissolve in the intestine, mucoadhesive polymers that prolong residence time, and ligands for receptors on enteroendocrine or epithelial cells[29]. Some carriers are designed to remain in the gastrointestinal lumen, delivering lipase inhibitors or microbiota-directed agents without significant systemic absorption, thereby minimizing off-target toxicity[29]. Others are tuned for trans-epithelial transport to reach lamina propria immune cells or portal circulation.

CNS targeting, particularly the hypothalamus, remains challenging due to the blood–brain barrier (BBB). However, a few circumventricular regions involved in metabolic regulation are more permeable[30]. Smart nanocarriers may exploit receptor-mediated transcytosis (e.g., transferrin receptor, insulin receptor) to cross the BBB, using ligands or antibodies on their surface. Nose-to-brain delivery via intranasal nanoparticles offers an alternative route. CNS-targeted nano-systems could deliver neuropeptides, receptor modulators, or gene therapies to normalize appetite and energy expenditure control, but safety requirements are high given the sensitivity of brain tissue[30, 31].

Multi-organ targeting is also possible. For example, a nanocarrier might be primarily designed for liver uptake but still show partial adipose accumulation, indirectly coordinating improvements in hepatic and adipose function[32]. However, such "polypharmacology by distribution" must be carefully managed to avoid unanticipated interactions. In all cases, ligand density, affinity, and carrier properties must be optimized together to achieve sufficient on-target delivery while limiting off-target uptake by the mononuclear phagocyte system, kidneys, and other non-metabolic tissues.

4. Stimuli-Responsive and Logic-Gated Nanocarriers in Obesity Therapy

Stimuli-responsive nanocarriers add temporal and contextual precision to targeted delivery. In obesity, relevant stimuli include both endogenous cues from diseased tissues and exogenous signals applied by clinicians[22, 33, 34].

Endogenous stimuli such as pH, redox state, enzymes, and mechanical stress differ between healthy and obese tissues[35]. Inflamed adipose and fatty liver often exhibit mildly acidic extracellular pH and elevated levels of reactive oxygen species (ROS). pH-sensitive polymers—containing acid-labile linkers or ionizable groups—can remain stable in blood (pH ~7.4) but swell, degrade, or release cargo at lower pH. Similarly, redox-responsive linkers with disulfide bonds cleave in the reductive intracellular milieu or ROS-sensitive moieties respond to oxidative stress, releasing drugs more rapidly in disease-associated environments[35].

Enzyme-responsive systems leverage overexpressed proteases or lipases in obese tissues. Peptide linkers susceptible to matrix metalloproteinases (MMPs) or specific adipose lipases can tether drugs to the carrier or

maintain a "stealth" coating until they encounter the target tissue, where enzymatic cleavage exposes a targeting ligand or triggers release. Such designs effectively link drug release to active pathological processes[36].

Externally triggered systems provide on-demand control. Photothermal and photo-responsive nanoparticles absorb NIR light, converting it to heat or undergoing chemical changes that liberate cargo[37]. Focused NIR irradiation can be applied to selected fat depots, enabling spatially confined activation of lipolytic or thermogenic agents. Ultrasound-responsive carriers, including gas-filled microbubbles and phase-change droplets, can be disrupted or permeabilized by focused ultrasound, enhancing local drug release and tissue penetration. Magnetic nanoparticles respond to alternating magnetic fields with localized heating or mechanical forces, providing yet another modality for triggerable delivery[37].

Beyond simple "on–off" release, logic-gated nanocarriers aim to approximate Boolean operations. For example, a carrier might release its payload only when both low pH AND high ROS are present, reducing leakage in tissues that share one but not both features. This can be implemented using multiple labile linkers in series or parallel, or by combining structural elements that respond sequentially to distinct cues[38]. While still largely experimental, such designs could substantially improve specificity for diseased adipose or liver microenvironments.

Stimuli responsiveness can also modulate pharmacokinetic profiles. Carriers may be constructed to remain stable during circulation, then disassemble rapidly on reaching target tissues, or to provide biphasic release an initial priming dose followed by a sustained low-level release[22, 34]. These patterns may better match the pharmacodynamics of appetite modulation or metabolic reprogramming than constant exposure. However, stimuli-responsive systems introduce complexity in design, manufacture, and regulatory evaluation. The magnitude of endogenous stimuli can vary widely between patients, disease stages, and even different depots within the same person[39]. External triggers require appropriate devices, treatment planning, and safety monitoring. Thus, careful preclinical characterization and modeling are needed to ensure that smart behavior is robust, predictable, and clinically manageable[39].

5. Nano-Enabled Delivery of Small Molecule, Peptide, and Nucleic Acid Anti-Obesity Agents

Smart nanocarriers serve as versatile platforms for multiple classes of anti-obesity therapeutics, each with distinct challenges and opportunities.

Small molecule drugs including lipase inhibitors, PPAR agonists, AMPK activators, and thermogenic agents often suffer from poor solubility, low bioavailability, or off-target toxicity[40]. Encapsulation in lipid or polymeric nanoparticles can increase solubility, protect from first-pass metabolism, and reduce peak plasma concentrations. For example, a liver-targeted nanocarrier carrying a PPARα/δ agonist could preferentially modulate hepatic lipid oxidation and VLDL secretion while limiting effects on skeletal muscle or heart[40]. Similarly, adipose-targeted carriers loaded with β-adrenergic agonists or other browning agents concentrate thermogenic modulation in fat depots, reducing cardiovascular side effects.

Peptide and protein drugs, such as GLP-1 receptor agonists, dual or triple incretin agonists, FGF analogues, and appetite-regulating neuropeptides, are highly potent but vulnerable to degradation and often require parenteral injection[41]. Nano-formulations can shield them from proteolysis, enable alternative routes (e.g., oral, inhaled, intranasal), and adjust release kinetics. Depot-forming nanoparticles may provide sustained peptide levels with reduced injection frequency. Targeting ligands can focus peptide action on receptors in the gut, liver, or CNS, potentially lowering required dose and minimizing systemic exposure[41].

Nucleic acid therapeutics siRNA, antisense oligonucleotides, miRNA mimics/inhibitors, and mRNA expand the target space to genes that are not easily druggable at the protein level. For obesity, candidate targets include enzymes regulating lipogenesis, transcription factors controlling adipocyte differentiation, and signaling molecules in insulin pathways[42]. Lipid nanoparticles and polymeric carriers enable systemic delivery of these cargos, with organ specificity determined by composition and targeting ligands. Liver-directed RNA therapeutics are already in clinical use for other indications, providing a translational blueprint for metabolic applications[42].

Gene-editing tools such as CRISPR/Cas systems can, in principle, produce more durable modifications of metabolic pathways for example, reducing expression of a lipogenic enzyme or enhancing levels of a protective hormone[34, 43, 44]. Nanocarrier-mediated delivery of Cas mRNA/protein and guide RNAs can localize editing to hepatocytes or adipocytes. However, the permanence of such edits demands stringent safety evaluation and precise targeting.

Combination strategies further exploit nano-platform versatility. A single carrier might co-encapsulate a GLP-1 analogue and a liver-targeted small-molecule insulin sensitizer, harmonizing effects on appetite and hepatic glucose production[17, 45]. Alternatively, nucleic acids might be combined with small molecules for example, siRNA to reduce lipogenesis combined with a PPAR agonist to promote fatty acid oxidation achieving multi-level metabolic modulation. Smart release mechanisms can stagger the timing of different components, approximating physiologic sequences of hormonal signaling. Overall, nano-enabled delivery broadens what is possible with both existing and novel anti-obesity agents, increasing the likelihood that potent but previously impractical molecules can be translated into clinically viable therapies.

6. Precision Medicine: Patient Stratification, Diagnostics, and Adaptive Nano-Therapy

Precision medicine in obesity aims to match the right therapy to the right patient at the right time, based on individual variations in biology and environment [46]. Smart nanocarriers can be tightly integrated into this paradigm[47].

First, patient stratification requires robust phenotyping. Clinical parameters (BMI, waist circumference), imaging (MRI, CT, ultrasound), and biomarkers (lipids, liver enzymes, inflammatory markers) identify patterns such as "metabolically healthy obesity," visceral vs subcutaneous predominance, and presence of NAFLD or prediabetes[48]. Genetic and epigenetic markers further delineate subgroups with altered appetite regulation, energy expenditure, or adipocyte biology. Microbiome profiling reveals gut ecosystem variations that influence energy harvest and hormone secretion[48].

These data guide the choice of nano-therapy. For example, patients with severe hepatic steatosis and high liver stiffness may benefit most from liver-targeted nano-formulations of insulin sensitizers or lipogenesis inhibitors[49]. Individuals with low BAT activity might be prioritized for adipose-targeted thermogenic nano-agents[49]. Those with strong emotional or hedonic eating may be candidates for CNS-penetrant nano-formulations of neuropeptides or receptor modulators. Precision targeting reduces unnecessary exposure in organs not central to a given patient's disease pattern.

Second, diagnostic integration is a hallmark of smart nanomedicine. Theranostic nanoparticles, carrying both imaging contrast agents and drugs, can provide real-time information on biodistribution and target engagement[50]. For instance, a liver-targeted nano-agent might incorporate a clinically approved MRI contrast component; early imaging can confirm sufficient hepatic accumulation before escalating doses. Similarly, adipose-targeted nano-therapies may be paired with PET or NIR imaging reporters to visualize depot-specific uptake and correlate this with changes in metabolic parameters[50].

Third, adaptive dosing and scheduling can be informed by dynamic biomarker and imaging data. If imaging reveals suboptimal accumulation in target tissues, dosing regimens, targeting ligands, or formulation composition can be adjusted[51]. Biomarkers such as changes in fasting glucose, triglycerides, and inflammatory markers help distinguish responders from non-responders early. This feedback loop is more powerful when nanocarriers themselves embody the diagnostic component, reducing the need for separate tracer injections[51].

Fourth, combination and sequencing strategies can be personalized. A patient might initially receive a liver-targeted nano-therapy to reduce steatosis and improve insulin sensitivity; once liver function stabilizes, adipose- or CNS-targeted nano-agents might be added to further drive weight loss[52]. Alternatively, nano-formulated incretin therapy could be combined with microbiota-modulating nanocarriers in individuals with dysbiotic gut profiles[52].

To realize this vision, informatics and systems medicine tools are needed to integrate multi-omic, imaging, and clinical data. Machine learning models could predict which nano-formulations, targeting strategies, and stimuli-responsive features are most likely to be effective for a given patient. Ethical considerations around data privacy, algorithmic bias, and equitable access must be addressed in parallel[53]. Nevertheless, smart nanocarriers are well-suited to function as both therapeutic and diagnostic tools within a precision medicine framework for obesity.

7. Safety, Regulatory, and Implementation Challenges for Nano-Enabled Obesity Precision Therapies

Despite their promise, smart nanocarriers for obesity face substantial translational barriers.

Safety and tolerability are central concerns. Nanoparticles can accumulate in the liver, spleen, and kidneys, potentially causing long-term toxicity, especially with chronic administration. Inorganic materials may persist for years; even biodegradable polymers can trigger inflammation or local acidosis as they degrade[54, 55]. Immunogenic responses to nanoparticle components, including PEG or targeting ligands, may lead to hypersensitivity reactions or reduced efficacy over time. For gene and RNA therapeutics, off-target effects and unintended immune activation must be rigorously assessed. In the CNS, any nano-agent must clear exceptionally high safety thresholds[56].

Dose and exposure considerations differ from oncology, where high toxicity can be more acceptable due to disease severity[57]. In obesity, patients are often ambulatory and relatively stable; benefit–risk expectations are stricter. Small increments in weight loss do not justify major safety trade-offs. Thus, nano-therapies must demonstrate superior risk–benefit profiles compared to existing systemic drugs to gain acceptance[57].

Regulatory pathways for nanomedicines are still evolving. Agencies require a detailed characterization of critical quality attributes, size distribution, composition, drug loading, release profiles, and their relationship to in vivo behavior[58]. For stimuli-responsive and logic-gated systems, regulators will also expect evidence that smart behavior is predictable, controllable, and unlikely to fail catastrophically (e.g., massive premature drug release). Combination products that include both drug and device elements (e.g., nanoparticles plus external NIR or ultrasound devices) face additional complexity[58].

Manufacturing and cost present practical hurdles. Many smart nanocarriers are synthesized via complex, multi-step processes that are difficult to scale while maintaining reproducibility. Batch-to-batch variability can alter biodistribution and efficacy[59]. Robust, GMP-compliant processes must be established, and unit costs kept

sufficiently low to be viable in chronic disease markets. Bio-inspired systems such as exosomes pose special challenges due to the heterogeneity of source cells and cargo.

On the implementation side, clinicians and health systems must adapt to new workflows. Use of theranostic particles requires coordination between metabolic clinics, radiology, and pharmacy. External-stimulus-dependent therapies require access to appropriate devices and trained staff. Decision support systems using biomarker and imaging data will be needed to operationalize precision dosing. Training and clear guidelines will be essential to avoid misuse or overuse in populations where the benefit is uncertain.

Finally, ethical and equity considerations loom large. Advanced nano-precision therapies risk exacerbating disparities if they are expensive and concentrated in specialized centers. There is a danger of over-medicalizing obesity and diverting attention from upstream determinants such as food systems, socio-economic inequality, and built environments. Transparent communication with patients about benefits, risks, and the role of lifestyle and environmental interventions remains critical. Addressing these challenges will require iterative dialogue among scientists, clinicians, regulators, industry, and patient communities. If navigated successfully, smart nanocarriers have the potential to complement existing lifestyle, pharmacologic, and surgical interventions, filling an important gap in the therapeutic landscape.

CONCLUSION

Smart nanocarriers for targeted delivery of anti-obesity agents represent a promising convergence of nanotechnology, metabolic science, and precision medicine. By concentrating drugs in specific organs, sensing pathological microenvironments, responding to external cues, and integrating diagnostic capabilities, these systems can enhance efficacy while reducing off-target toxicity. Their versatility enables tailored delivery of small molecules, peptides, and nucleic acids, as well as rational combinations that address the multi-organ nature of obesity. However, translation into routine care demands rigorous attention to safety, manufacturability, regulatory requirements, and health system integration, alongside strong consideration of equity and ethical implications. As understanding of obesity heterogeneity and tissue-specific pathophysiology deepens, smart nanocarriers may form the basis of highly individualized metabolic therapies moving obesity management beyond one-size-fits-all pharmacology toward truly personalized, mechanism-guided intervention.

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