International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Advances in Microneedle Drug Delivery for Obesity: Mechanisms, Applications, and Perspectives

Chengyu Wu[1,*], Ziliang Zong[2,*], Feiran Hua[2], Jiong Wu[3], Yan Shen[3], Yu Tian[4], Yigang Chen[1,2]

[1]Department of General Surgery, The Affiliated Wuxi No. 2 Hospital of Nanjing Medical University, Wuxi, Jiangsu, 214002, People's Republic of China; [2]Jiangnan University Medical Center (Wuxi No.2 People' s Hospital), Wuxi, Jiangsu Province, 214000, People's Republic of China; [3]Department of Pharmaceutics, State Key Laboratory of Nature Medicines, School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, People's Republic of China; [4]School of Medicine, Shanghai University, Shanghai, 200444, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yu Tian; Yigang Chen, Email shu_yutian@shu.edu.cn; 9862023226@jiangnan.edu.cn

Abstract: Obesity is a multifactorial metabolic disorder associated with increased risks of diabetes, cardiovascular disease, and other comorbidities. Conventional pharmacological interventions are often limited by poor patient adherence, systemic side effects, and suboptimal drug bioavailability. Microneedle (MN)-based transdermal drug delivery systems have emerged as a promising alternative, offering minimally invasive, painless, and patient-friendly administration. MN platforms not only bypass gastrointestinal degradation and hepatic first-pass metabolism but also enable targeted delivery to adipose tissue, thereby reducing systemic toxicity. Recent studies have demonstrated the potential of MNs to deliver diverse therapeutic agents, including small molecules, peptides, nucleic acids, and nanoparticles, for regulating adipose tissue metabolism, modulating the inflammatory microenvironment, and promoting browning of white adipose tissue. Various MN designs, such as dissolving, hydrogel-forming, and stimuli-responsive systems, allow precise control over release kinetics, ranging from ultrarapid drug exposure to long-term sustained delivery. Despite these advantages, several key challenges hinder clinical translation, including limited drug loading capacity, interindividual variability in skin penetration, potential local skin reactions with chronic use, and the difficulty of scaling up MN fabrication to Good Manufacturing Practice (GMP) standards while maintaining reproducibility and quality. Future perspectives emphasize the integration of nanocarrier systems, artificial intelligence-driven MN design, and multifunctional wearable devices to achieve personalized and adaptive therapy. With continued technological and translational advances, MN-based delivery could enable a new approach for obesity treatment, pending robust clinical validation.

Keywords: obesity, microneedle, transdermal drug delivery, adipose tissue metabolism

Introduction

Obesity has emerged as a global health epidemic, with its prevalence continuously rising across both developed and developing countries. According to the World Health Organization (WHO), more than one billion individuals worldwide are classified as obese, a condition strongly associated with severe comorbidities including type 2 diabetes mellitus (T2DM), cardiovascular diseases, nonalcoholic fatty liver disease, and certain types of cancer.[1–4] These complications not only increase morbidity and mortality but also place a tremendous burden on healthcare systems.

Current therapeutic strategies for obesity encompass lifestyle interventions, pharmacotherapy, and bariatric surgery.[5] While lifestyle modification remains the cornerstone, its long-term efficacy is often limited by poor adherence. Pharmacological treatments, such as appetite suppressants, lipase inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, offer metabolic benefits but face considerable challenges including low oral bioavailability, rapid systemic metabolism, gastrointestinal side effects, and the need for frequent injections that compromise patient compliance.[6–8] Bariatric surgery, though effective, is invasive and associated with perioperative risks, limiting its widespread applicability.[9] Hence, there is an urgent need for alternative delivery strategies that are safe, effective, and patient-friendly.

Received: 8 September 2025
Accepted: 2 December 2025
Published: 18 December 2025

Microneedles (MNs)-based drug delivery systems have attracted increasing attention as a promising approach to address these limitations.[10,11] MNs, characterized by their minimally invasive and virtually painless penetration into the skin, enable the transdermal delivery of a broad spectrum of therapeutics ranging from small molecules to peptides, proteins, and nucleic acids.[12,13] Their unique advantages include improved drug stability by bypassing gastrointestinal metabolism, enhanced patient compliance due to their noninvasive nature, and the capacity for controlled or sustained release.[14,15] Furthermore, the cutaneous and subcutaneous microenvironment offers opportunities for localized delivery to adipose tissue or systemic absorption without the drawbacks of conventional injection routes.[16,17] Compared with conventional oral and transdermal delivery, MNs provide superior delivery efficiency by directly breaching the stratum corneum barrier, overcoming the limited permeability of passive diffusion systems. Unlike oral administration, which often suffers from poor bioavailability and gastrointestinal degradation, or traditional transdermal patches that rely solely on concentration gradients, MNs enable precise, reproducible, and programmable drug transport into targeted tissue layers. Based on data from ClinicalTrials.gov, several clinical trials have investigated obesity treatment using transdermal patch systems. For instance, a study evaluated the effects of percutaneous electrical neurostimulation (PENS) of dermatome T6 with an ambulatory self-applied patch on appetite and weight loss in moderately obese patients (NCT02564627).[18] Another trial assessed the efficacy and safety of the Elira wearable patch system for weight loss (NCT03299881).

This review aims to provide a comprehensive overview of MN-based drug delivery for obesity therapy. We first summarized the design principles and functional categories of MNs, followed by a discussion of therapeutic targets relevant to obesity management. Representative mechanistic strategies and recent preclinical advances in MNs-mediated obesity therapy are then highlighted. Finally, we analyzed the advantages, translational challenges, and future perspectives of this emerging platform, with an emphasis on its potential to reshape the therapeutic paradigm for obesity (Figure 1).

MNs-Based Drug Delivery Systems

Classification of MNs

MNs are micron-scale projections, typically 150–1500 μm in length, designed to painlessly pierce the stratum corneum (SC) without reaching the deeper dermis or stimulating nociceptors.[19] Based on their structure and delivery mechanism, MNs are generally classified into five categories: (a) Solid MNs. Commonly fabricated from silicon, metals, or polymers, solid MNs are primarily used in a "poke-and-patch" strategy.[20] They first create transient microchannels in the skin, through which drug-loaded patches or topical formulations subsequently diffuse.[21] While simple and cost-effective, this approach requires an additional formulation step and may result in variable drug permeation.[22] (b) Coated MNs. Drugs are applied directly onto the MNs surface by techniques such as dip-coating, spray-coating, or layer-by-layer deposition.[23] Upon insertion, the coating dissolves rapidly, enabling precise dosing and rapid onset. However, the limited surface area restricts drug loading capacity.[24] (c) Hollow MNs. Featuring a central lumen, hollow MNs permit direct injection of liquid formulations into the skin, allowing administration of larger drug volumes and macromolecular therapeutics (eg, peptides and proteins).[25] Nonetheless, their relatively complex fabrication and risk of lumen blockage during insertion remain challenges.[26] (d) Dissolving MNs. Constructed from biocompatible and water-soluble polymers such as hyaluronic acid (HA), carboxymethylcellulose (CMC), or polyvinylpyrrolidone (PVP), these MNs encapsulate the therapeutic payload within the polymer matrix and dissolve completely in the skin.[27] Dissolving MNs are particularly relevant for obesity therapy, as they provide safe, needle-free delivery of biomolecules while eliminating sharp waste disposal concerns.[28] (e) Hydrogel-forming MNs. Fabricated from cross-linked polymers such as gelatin methacrylate or poly(ethylene glycol) diacrylate (PEGDA), hydrogel MNs swell upon absorbing interstitial fluid, forming a continuous conduit for sustained drug diffusion from a backing reservoir.[29,30] Their mechanical robustness, reversibility, and ability to provide controlled release make them well-suited for long-term management of chronic diseases including obesity (Figure 2).[31]

Overall, each MN type offers unique advantages and limitations, and the choice of system for obesity therapy depends on drug physicochemical characteristics, desired pharmacokinetics, and specific therapeutic targets.

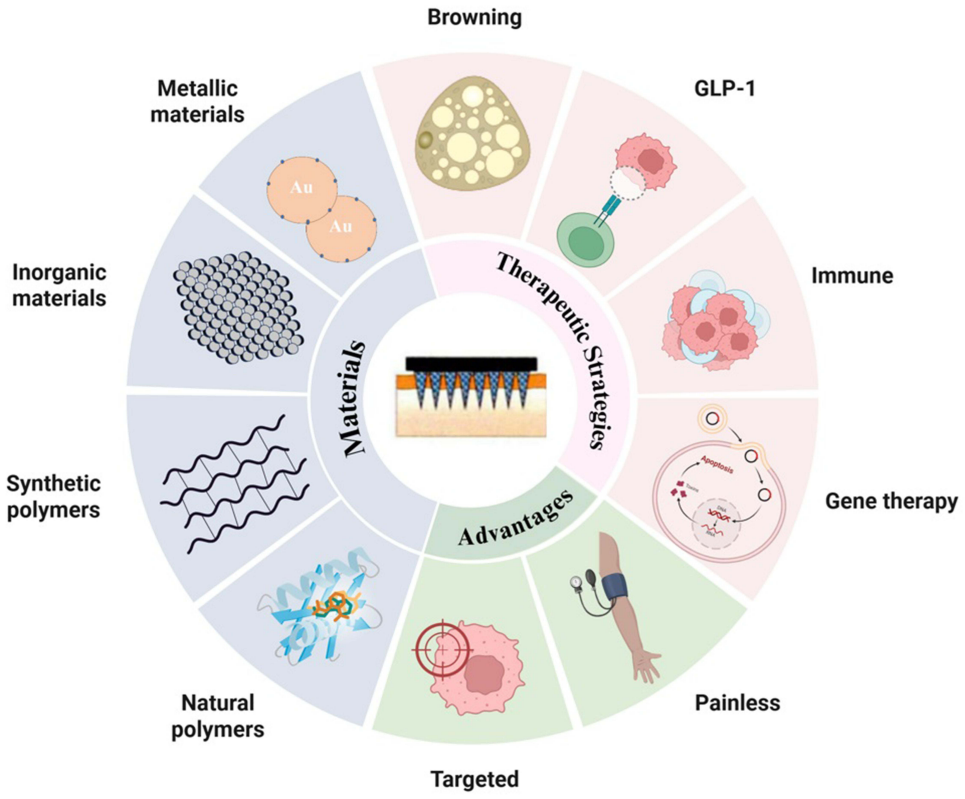

Figure 1 Schematic illustration of MN-based drug delivery systems for obesity treatment, highlighting the fabrication materials, therapeutic advantages, and representative strategies.

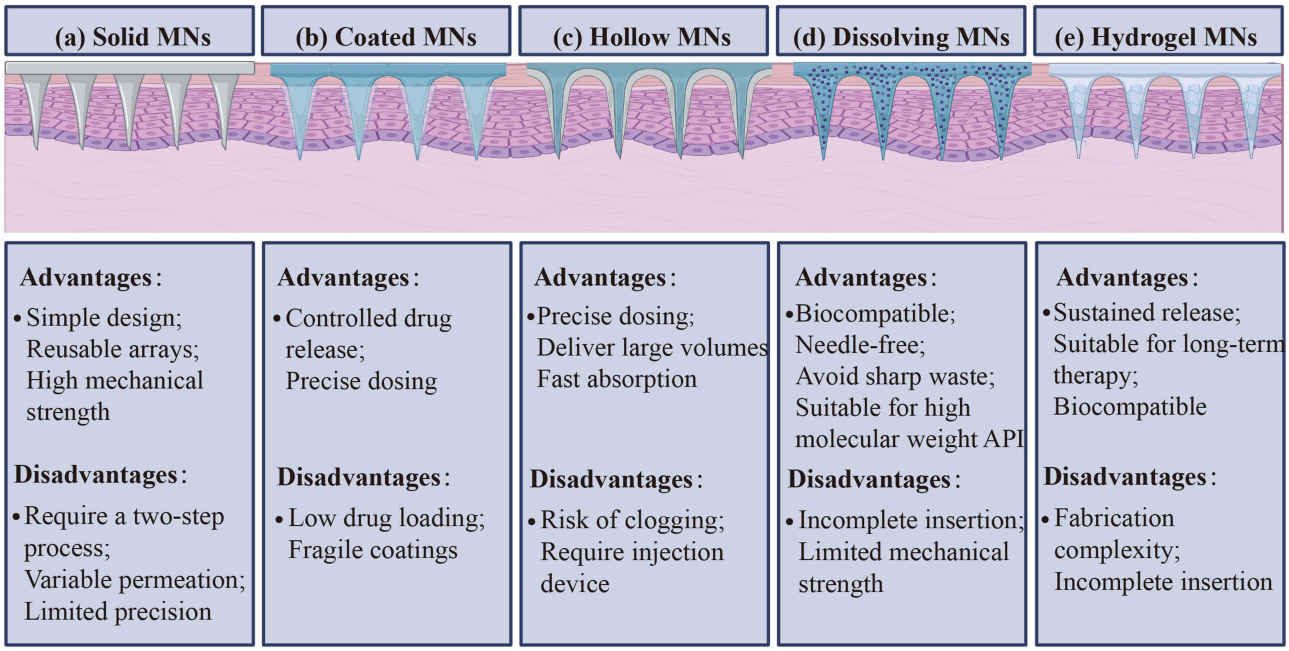

Figure 2 Schematic illustration of different types of MNs: (**a**) solid MNs, (**b**) coated MNs, (**c**) hollow MNs, (**d**) dissolving MNs, and (**e**) hydrogel MNs, along with their respective advantages and limitations. Created with https://BioRender.com.

https://doi.org/10.2147/IJN.S566132

Materials Used in MNs Fabrication

The selection of materials plays a pivotal role in determining the mechanical strength, biocompatibility, drug-loading capacity, and release kinetics of MNs. Broadly, materials can be classified into natural polymers, synthetic polymers, and inorganic or metallic materials, each offering distinct properties for obesity therapy applications.

Natural Polymers

Natural polymers are among the most extensively used materials for MNs fabrication due to their intrinsic biocompatibility, biodegradability, and ability to encapsulate and preserve the bioactivity of sensitive biomolecules.[32] Sugars such as pullulan, maltose, and trehalose have been widely employed to prepare dissolvable MNs, primarily owing to their rapid dissolution rate and efficient release of the loaded drug payload upon skin insertion.[15,33] However, their relatively low mechanical strength often limits penetration efficiency. Polysaccharides including sodium chondroitin sulfate, dextran, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), CMC, sodium alginate, and amylopectin provide a versatile platform for MN fabrication.[34,35] Their hydrophilic functional groups (eg, hydroxyl, carboxyl, or sulfo groups) and branched structures confer excellent solubility and make them particularly suitable for loading water-soluble compounds. Moreover, drugs embedded within polysaccharide-based MN matrices generally retain bioactivity and can achieve controlled release, while maintaining sufficient mechanical strength for effective skin penetration.[36,37] HA is one of the most popular polysaccharides used in MNs because of its high solubility, safety profile, and ability to encapsulate peptides or nucleic acids without compromising stability.[38,39] Similarly, chitosan and its derivatives have been investigated for their biocompatibility, antimicrobial properties, and prolonged degradation profiles, which allow sustained drug release.[40] Proteins such as gelatin and silk fibroin have also been employed to fabricate dissolvable or hydrogel-forming MNs.[41] Gelatin offers tunable gel strength and biodegradability, making it suitable for versatile applications.[42] Silk fibroin, when used as multilayered structures combined with polymers such as polyvinyl alcohol (PVA), provides high mechanical strength and rapid dissolution, while also ensuring stability at room temperature during storage.[43]

Overall, natural polymers offer unique advantages including biocompatibility, safety, and versatility in controlling drug release kinetics. By carefully selecting or combining natural polymers, MNs can be tailored to achieve rapid release, sustained delivery, or targeted therapeutic outcomes, which is particularly valuable in obesity therapy where chronic and controlled intervention is required.

Synthetic Polymers

Synthetic polymers are widely employed in MNs fabrication due to their tunable physicochemical properties, controlled dissolution and swelling behavior, and potential for sustained drug release.[44] Compared with natural polymers, synthetic polymers offer greater flexibility in regulating mechanical strength, degradation kinetics, and release profiles, which makes them highly suitable for tailoring MNs systems to specific therapeutic needs.[45]

Poly(lactic-co-glycolic acid) (PLGA), an FDA-approved biodegradable polymer, is one of the most extensively studied materials for controlled-release MNs. Its hydrolytic degradation generates lactic and glycolic acids, which are naturally metabolized in the body. By embedding hydrogel microparticles or modifying fabrication strategies, PLGA-based MNs can achieve long-term sustained release through passive diffusion, lasting for weeks to months.[46] PVP and poly(methyl vinyl ether-co-maleic anhydride) (PMVE/MA) are water-soluble polymers frequently used for dissolving MNs. Their rapid dissolution upon skin insertion allows efficient release of hydrophilic drugs, although hydrophobic drugs often exhibit limited solubility in these matrices. To overcome mechanical limitations, copolymerization or blending strategies have been employed.[47] Similarly, incorporating cyclodextrin into PVP matrices enhanced mechanical strength via hydrogen bonding and improved drug loading efficiency.[48] PVA is another versatile synthetic polymer that combines mechanical robustness with unique phase transition properties. Under freeze–thaw cycles, PVA forms microcrystalline cross-linked hydrogels, which can encapsulate and protect sensitive biomolecules such as insulin.[49] These structural features allow PVA MNs to provide both immediate release and extended delivery profiles, depending on formulation design.[50] Novel fabrication approaches, including electro-drawing techniques for PLGA, further expand the

potential of synthetic polymers by enabling the incorporation of both hydrophobic and hydrophilic drugs into microstructured matrices.[51]

Despite these advantages, the use of synthetic polymers also faces challenges. Their fabrication often involves organic solvents or elevated temperatures, which may compromise the stability of sensitive therapeutic agents such as peptides, proteins, or nucleic acids.[52] Moreover, the limited drug-loading capacity inherent to polymer matrices can constrain their therapeutic efficacy, particularly for obesity interventions requiring higher doses or sustained release of macromolecules. Nevertheless, with continued innovations in polymer engineering and fabrication techniques, synthetic polymers remain highly promising materials for the development of dissolving and hydrogel-forming MNs in transdermal drug delivery.[53]

Inorganic and Metallic Materials

Inorganic and metallic materials, such as silicon, stainless steel, titanium, and ceramic composites, have been widely explored in the fabrication of MNs, particularly for solid and hollow designs.[54,55] Their primary advantages lie in excellent mechanical strength, durability, and the ability to achieve highly precise microstructures through advanced microfabrication techniques, including photolithography and etching.[56] These properties make them especially suitable for applications requiring reliable penetration of the stratum corneum and precise control over drug flow in hollow MN systems.[57] Silicon-based MNs were among the first to be developed due to the maturity of semiconductor processing techniques, which allow accurate control over geometry, sharpness, and size distribution.[58] However, their inherent brittleness increases the risk of needle fracture during insertion, raising safety concerns for clinical use. Similarly, stainless steel and titanium MNs offer superior tensile strength and have been employed in both research and commercial devices.[59] Titanium, in particular, provides better corrosion resistance and biocompatibility than stainless steel, making it more favorable for long-term contact with biological tissues.[60]

Despite these advantages, the lack of biodegradability and concerns regarding long-term biocompatibility significantly limit the application of inorganic and metallic MNs in chronic disease management such as obesity therapy.[56] Retained non-degradable materials may pose risks of local irritation, foreign body response, or long-term tissue accumulation. Moreover, their inability to encapsulate and release sensitive biomacromolecules, such as peptides, nucleic acids, or nanoparticles, restricts their utility for advanced therapeutic strategies.

Release Kinetics and Controlled Drug Release

Controlled drug release is a pivotal requirement in obesity therapy, which often involves chronic and long-term interventions. MNs-based systems offer versatile platforms that can be engineered to achieve distinct release kinetics depending on their structural design and material composition.[61]

A first strategy is rapid release, typically achieved with coated or dissolving MNs. These systems release their payload within minutes to several hours after insertion, enabling rapid drug absorption and fast pharmacological effects.[62,63] Such profiles are particularly advantageous for agents requiring immediate systemic exposure, including short-acting lipolytic drugs or appetite suppressants. In contrast, sustained release is enabled by hydrogel-forming MNs and biodegradable polymer-based MNs (eg, PLGA).[64] These designs allow prolonged drug delivery over several days to weeks, which is highly desirable for obesity management. By reducing dosing frequency and maintaining steady therapeutic concentrations, sustained-release systems improve patient adherence and provide more consistent metabolic control.[65] Beyond these conventional strategies, stimuli-responsive release represents an emerging frontier. Smart MNs fabricated with temperature-, pH-, enzyme-, or glucose-sensitive polymers can dynamically adjust drug release in response to local biochemical or metabolic cues.[66,67] For example, self-assembled stearic acid–modified chitosan oligosaccharide (COA) nanoparticles were engineered to efficiently promote the degradation of lipid droplets in adipocytes via autolysosomal pathways. Microneedles incorporating these COA nanoparticles, combined with photothermal therapy, were shown to significantly reduce body weight and white adipose tissue mass in obese mice, without altering their food intake.[68] This adaptive property is particularly beneficial in obese patients with comorbidities such as T2DM, where feedback-regulated delivery can synchronize therapeutic exposure with metabolic fluctuations, thereby optimizing efficacy while minimizing side effects.

In summary, the ability to fine-tune release kinetics, from rapid burst to sustained and stimuli-responsive profiles, enables MNs-based platforms to accommodate a wide spectrum of anti-obesity therapeutics, ranging from short-acting β3-adrenergic agonists to long-acting GLP-1 receptor agonists and nucleic acid-based drugs. This flexibility underscores their potential to establish personalized and effective treatment regimens in obesity care.

Advantages of MNs for Obesity Therapy

Compared with conventional oral and injectable routes, MNs-based systems provide several distinctive advantages that are particularly relevant for the long-term and multifactorial management of obesity. These advantages can be summarized into the following key aspects:

Improved Bioavailability and Suitability for Biologics

Many anti-obesity agents, including GLP-1 receptor agonists, peptide hormones, and nucleic acid-based therapeutics, suffer from poor oral bioavailability due to enzymatic degradation in the gastrointestinal tract and extensive first-pass hepatic metabolism.[69] MNs overcome these limitations by bypassing the digestive system and delivering drugs directly across the skin.[26] This not only preserves biological activity but also expands therapeutic options to include fragile macromolecules such as peptides, proteins, and RNA-based drugs, which are otherwise unsuitable for oral delivery.

Painless and Patient-Friendly Administration

Chronic obesity treatment often requires long-term, frequent dosing, which makes adherence a major challenge. Traditional subcutaneous injections are associated with discomfort, needle phobia, and the risk of sharp waste disposal, all of which reduce patient compliance. By contrast, MNs penetrate only the stratum corneum without reaching deep pain receptors, offering a virtually painless, minimally invasive route of administration. This patient-friendly feature is particularly valuable for self-administration in chronic conditions, ultimately improving adherence and long-term treatment outcomes.[70]

Targeted and Localized Drug Delivery

One unique advantage of MNs lies in their ability to deliver therapeutics directly into subcutaneous adipose depots, enabling high local concentrations at the intended site of action while minimizing systemic exposure.[17] Such localized targeting is especially relevant for interventions aimed at inducing browning of white adipose tissue, modulating inflammatory responses within fat tissue, or activating metabolic pathways in situ.[71] By restricting drug distribution to the relevant tissue compartment, MNs can enhance therapeutic efficacy while reducing systemic side effects, such as gastrointestinal intolerance or cardiovascular complications.

Controlled and Sustained Release for Chronic Therapy

The chronic nature of obesity demands delivery systems that can maintain therapeutic drug levels over extended periods. In the context of obesity, where treatment may extend for months or years, sustained-release MNs are particularly advantageous in ensuring stable pharmacological action without the burden of repeated injections.

Potential for Smart and Personalized Therapy

Beyond conventional drug release, MNs can be engineered with stimuli-responsive materials and integrated with wearable or diagnostic technologies to enable dynamic, feedback-regulated drug delivery.[72] For example, glucose-responsive MNs have been designed to modulate GLP-1 analog release in response to fluctuating glucose levels, thereby addressing both obesity and T2DM in a personalized, demand-driven manner. This adaptability represents a transformative step toward precision medicine in metabolic disorders, enabling tailored treatment strategies that align with individual patient needs and metabolic states.

In summary, MN-based delivery systems provide a versatile, patient-centric platform that addresses many limitations of oral and injectable therapies. Their ability to enhance the bioavailability of fragile biomolecules, improve patient

adherence, target adipose tissue locally, provide long-term controlled release, and enable smart personalized treatment highlights their translational potential in obesity therapy.[16,73]

Strategies of MNs-Assisted Obesity Therapy

Recent studies have demonstrated that MN systems can be engineered to intervene at multiple pathological levels of obesity. Current strategies primarily focus on regulating adipose tissue metabolism through induction of browning, modulating hormonal and gut–brain axes (eg, GLP-1, GIP, insulin), reshaping the inflammatory and immune microenvironment, and enabling emerging approaches such as gene therapy, photothermal modulation, and iontophoresis-assisted delivery (Table 1). Together, these approaches highlight the versatility of MN-based platforms in addressing the multifactorial mechanisms underlying obesity.

Regulating Adipose Tissue Metabolism

Adipose tissue is central to energy balance, functioning not only as a storage depot for excess calories but also as a metabolically active organ that regulates systemic homeostasis. White adipose tissue (WAT) primarily stores triglycerides in large unilocular lipid droplets, contributing to weight gain and metabolic dysfunction when accumulated in excess. In contrast, brown adipose tissue (BAT) dissipates energy as heat through non-shivering thermogenesis, mediated by mitochondrial uncoupling.[80]

A major breakthrough in obesity research has been the discovery of WAT browning, wherein white adipocytes convert into thermogenically active beige adipocytes.[81] Although derived from the same lineage as WAT, beige adipocytes share morphological and functional characteristics with BAT, including multilocular lipid droplets, abundant mitochondria, and high expression of uncoupling protein 1 (UCP1).[82,83] UCP1 is a pivotal mitochondrial protein that

Table 1 Summary of MNs-Assisted Strategies for Obesity Therapy

Strategy	Main Advantages	Main Limitations	Stage of Development	Key Therapeutic Outcomes
1) WAT Browning	• Promotes conversion of WAT to energy-burning BAT • Increases thermogenesis and energy expenditure	• Effect may be transient • Localized delivery may limit systemic efficacy	In vivo (mouse)	• 10–20% body weight reduction in 4–6 weeks[16,74] • UCP1 expression increase[74]
2) GLP-1 peptide and analogs delivery	• Sustained appetite suppression • Improved glucose tolerance and lipid metabolism	• Peptide instability • Requires controlled-release design to maintain plasma levels	In vivo (mouse)	• Food intake and fasting glucose decrease[63]
3) Regulating inflammatory microenvironment	• Targets obesity-associated chronic inflammation (eg, TNF-α, IL-6) • Reduces macrophage infiltration in WAT	• Anti-inflammatory effect may not directly trigger weight loss • Long-term immunomodulatory safety unclear	In vivo (mouse)	• Inflammatory cytokines by >50% • Mild weight loss and improved metabolic profiles[74]
4) Gene therapy (RNAi, shRNA, CRISPRi/CRISPRa)	• Enables precise modulation of metabolic or thermogenic genes • Potential for longer-lasting effects	• Risk of off-target effects • Complex formulation and stability issues	In vivo (mouse)	• Up to 20–30% weight reduction with long term body weight loss after ceasing treatment[75,76]
5) PTT combined with MNs	• Enables controlled lipolysis under NIR irradiation • Can be combined with thermogenic agents	• Requires external energy source (laser) • Potential for local overheating or skin irritation	In vivo (mouse)	• Local fat layer reduction by 30–40%[68] • Around 15%–20% total body weight loss[77]
6) MNs Combined with Iontophoresis	• Enhances transdermal transport efficiency via electric field-assisted permeation • Suitable for peptides, nucleic acids, and hydrophilic compounds	• Device complexity • Possible skin irritation with chronic use • Need for portable power source	In vivo (mouse)	• Higher transdermal drug delivery efficiency[78] • 20–25% weight reduction vs passive MNs[79]

https://doi.org/10.2147/IJN.S566132

uncouples oxidative phosphorylation, dissipating the proton gradient as heat rather than ATP, thereby increasing fatty acid oxidation and energy expenditure.[84,85] The upregulation of UCP1-driven thermogenesis thus represents a promising target for obesity treatment. The browning process is regulated by a complex network of transcription factors and signaling pathways. Among these, peroxisome proliferator-activated receptor γ (PPARγ) plays a key role in driving beige adipocyte differentiation.[86] Pharmacological agonists such as rosiglitazone can enhance mitochondrial biogenesis and upregulate UCP1 expression. Other regulators, including β3-adrenergic receptor agonists and PGC-1α, further promote oxidative metabolism and thermogenesis, reinforcing the metabolic benefits of WAT browning.[87]

Despite their therapeutic potential, conventional browning agents often lack tissue selectivity and may induce systemic side effects, limiting clinical translation. MNs-based delivery systems offer a solution by enabling localized, sustained, and controlled release of browning agents directly into subcutaneous adipose depots. This approach maximizes efficacy while minimizing off-target risks. For example, Gu's group designed a MN-based transcutaneous patch that incorporated degradable nanoparticles loaded with browning agents such as rosiglitazone or CL 316243 (Figure 3A).[16] The system provided sustained, glucose-responsive release of therapeutics into subcutaneous adipocytes, promoting WAT-to-beige transformation, enhancing thermogenesis, and increasing whole-body energy expenditure. Importantly, localized delivery restricted drug action to treated fat depots, thereby reducing systemic side effects. In a diet-induced obese mouse model, the patch significantly reduced local fat pad size, enhanced fatty acid oxidation, improved insulin sensitivity, and achieved marked weight reduction. More recently, Chen et al reported the development of a soluble hyaluronic acid-based MN patch (HORN-MN) for co-delivery of rosiglitazone and oleanolic acid (Figure 3B).[74] Upon rapid dissolution in the abdominal dermis, nanoparticles were internalized by macrophages and adipocytes, where lysosomal degradation released the active compounds. Oleanolic acid alleviated adipose inflammation by driving macrophage polarization toward the anti-inflammatory M2 phenotype and suppressing tumor necrosis factor-α (TNF-α) secretion, while rosiglitazone activated the PPARγ pathway, increased PGC-1α and UCP1 expression, and promoted WAT browning. Through this synergistic mechanism, HORN-MN significantly enhanced adipose tissue browning and achieved pronounced anti-obesity effects in mice, with body weight reductions of up to 17%.

In summary, MN-based delivery of browning agents represents a powerful strategy to reprogram adipose tissue metabolism by promoting WAT-to-beige conversion and enhancing thermogenesis. This localized and controlled approach not only improves efficacy but also reduces systemic risks, positioning MNs as a promising platform for metabolic intervention in obesity.

GLP-1 in Obesity Therapy

GLP-1 and its analogs have emerged as highly effective pharmacological interventions for obesity, particularly given the strong association between obesity and T2DM.[88] Since T2DM is a common comorbidity of obesity, therapies that simultaneously improve glycemic control and reduce body weight are of great clinical value. GLP-1–based treatments offer a non-invasive and well-tolerated alternative to surgical or other invasive interventions, aligning with patient preference, especially in the early to moderate stages of disease progression.[89]

Among GLP-1 analogs, liraglutide (LRT) is a recombinant peptide engineered for prolonged half-life and enhanced stability. Structurally, it consists of a GLP-1 backbone conjugated at Lys26 to a C-16 fatty acid chain via a glutamic acid spacer, while a K34R substitution ensures site-specific conjugation.[90] This modification allows LRT to bind circulating albumin, protecting it from rapid enzymatic degradation and renal clearance, and enabling once-daily administration.[74] Mechanistically, LRT binds GLP-1 receptors located in the pancreas, gastrointestinal tract, and central nervous system.[91] Through these interactions, it enhances glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying, and suppresses appetite via central satiety pathways.[92] Collectively, these effects reduce body weight, improve glycemic control, lower blood pressure, and ameliorate dyslipidemia, establishing LRT as an effective therapy for obesity and T2D.

Although traditionally administered via subcutaneous injection, LRT treatment can cause gastrointestinal side effects, generate biohazardous waste, and lead to local complications such as lipoatrophy, inflammation, or subcutaneous nodules.[93] Moreover, repeated injections often reduce patient adherence, limiting long-term efficacy. To overcome these challenges, MN-assisted delivery systems have been developed to enhance patient compliance and optimize

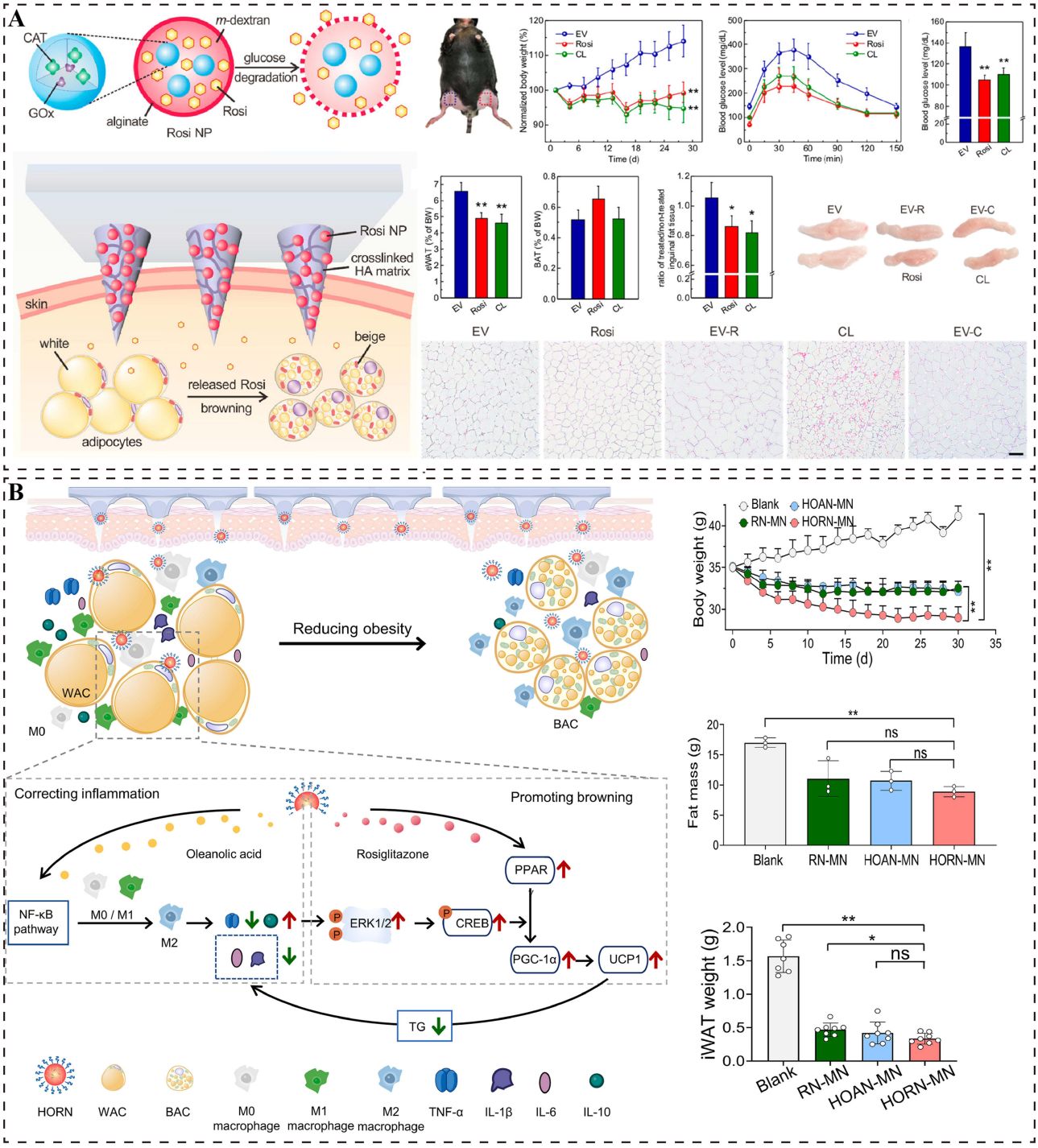

Figure 3 MN-mediated strategies for inducing WAT browning in obese mice. (**A**) Browning reagent–loaded transcutaneous MN patch delivers agents locally to subcutaneous adipose tissue, promoting WAT browning, reducing body weight, improving glucose tolerance, and alleviating adiposity in high-fat diet (HFD)–induced obese mice. Scale bar: 50 μm. Significance is denoted as ns $p > 0.05$. *$p < 0.05$. **$p < 0.01$. Reproduced with permission.[16] Copyright 2017, ACS Publications. (**B**) HORN-MN patch enables transdermal delivery of nanoparticles to subcutaneous adipose tissue, modulating lipid metabolism and inducing WAT browning. In HFD–induced obese mice, treatment decreases body weight gain and adiposity while improving metabolic parameters. Significance is denoted as ns $p>0.05$. *$p < 0.05$. **$p < 0.01$. Reproduced with permission.[74] Copyright 2024, Elsevier.

therapeutic outcomes. For instance, a PVP-based dissolving MN (DMN) patch incorporating PLGA nanoparticles was designed for minimally invasive LRT administration (Figure 4A).[94] Embedding nanoparticles not only improved MN mechanical strength compared with DMNs loaded with free LRT but also enabled controlled, sustained release. The PLGA nanoparticles provided a biphasic release profile lasting up to 15 days, with nearly 80% of the payload released

https://doi.org/10.2147/IJN.S566132

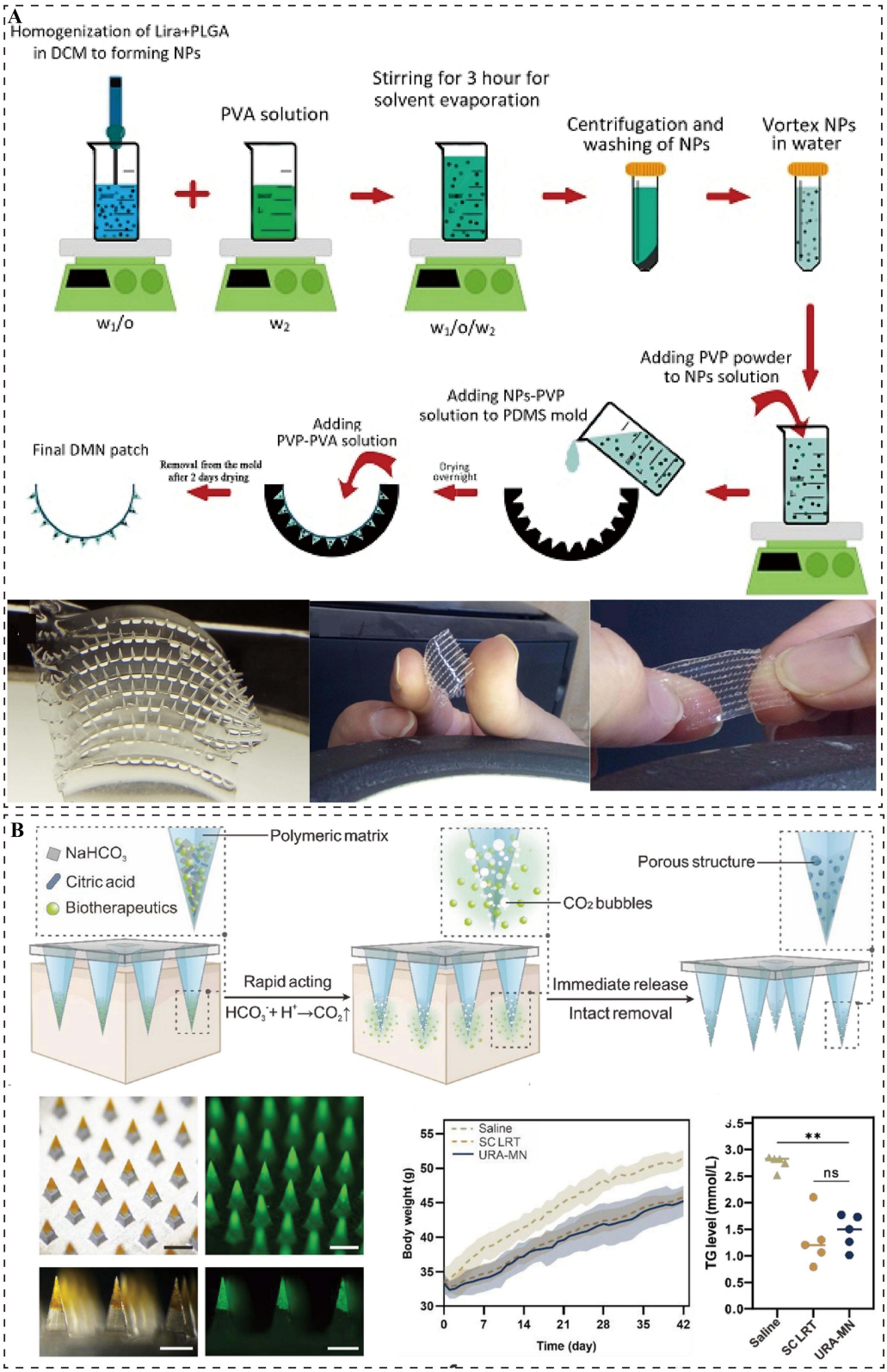

Figure 4 (**A**) Schematic illustration of DMN fabrication containing Lira-PLGA nanoparticles. DMN arrays unsealed from the PDMS mold. Demonstration of flexibility in the bent mode. DMN arrays displayed in the flat mode. Reproduced with permission.[94] Copyright 2021, Elsevier. (**B**) Schematic illustration and evaluation of the URA-MN patch for immediate delivery of biotherapeutics. Mechanism of ultrarapid drug release: upon insertion into the skin, embedded effervescent agents dissolve and react to generate CO_2, which accelerates the release of the loaded drug. Therapeutic evaluation of LRT-loaded URA-MN patch in db/db mice (n = 5) over 6 weeks; plasma glucose levels following daily treatments with saline, subcutaneous LRT (1.00 mg/kg), or MN patches (1.73 mg/kg); HbA1c levels at six weeks post-treatment; body weight monitoring during the treatment period. Scale bars: 1 mm (top), 500 μm (bottom). Significance is denoted as ns $p>0.05$. **$p < 0.01$. Reproduced with permission.[63] Copyright 2023, Wiley-VCH Verlag.

within the first 8 days. This hybrid nanoparticle–MN system demonstrated efficient drug loading, robust mechanical integrity, and consistent dose delivery, representing a promising approach for sustained, patient-friendly LRT therapy in obesity management. In addition, an ultrarapid-acting MN (URA-MN) patch has been developed to achieve immediate transdermal drug release (Figure 4B).[63] Incorporating effervescent agents in the MN tips generates CO_2 bubbles upon insertion, rapidly delivering therapeutics such as LRT within just five minutes. In diet-induced obese mouse models, URA-MN treatment effectively reduced body weight, achieving results comparable to conventional subcutaneous injection. Importantly, after six weeks of administration, serum triglyceride levels decreased from 2.75 mmol/L in saline-treated controls to 1.45 mmol/L in the URA-MN group, approaching the normal physiological range.

In summary, GLP-1 analogs delivered via MN platforms offer versatile and minimally invasive strategies to promote weight loss, improve metabolic parameters, and enhance patient compliance. These approaches underscore the translational potential of MN-based systems for optimizing GLP-1–mediated obesity therapy.

Inflammation Microenvironment in Obesity

Chronic low-grade inflammation within WAT is a hallmark of obesity and a critical driver of its metabolic complications. Excess triglyceride accumulation in hypertrophic adipocytes induces hypoxia and endoplasmic reticulum stress, which recruit pro-inflammatory M1 macrophages. These macrophages secrete cytokines such as TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6), thereby exacerbating local inflammation and impairing adipocyte browning by suppressing UCP1 expression and mitochondrial uncoupling, ultimately promoting fat accumulation.[95,96]

The imbalance between M1 and anti-inflammatory M2 macrophages further shapes the immune microenvironment. In obese adipose tissue, an elevated M1/M2 ratio enhances the production of angiogenic mediators such as platelet-derived growth factor (PDGF), which disrupts vascular remodeling and contributes to pathological tissue expansion.[97,98] Moreover, chronic hyperglycemia and inflammatory stimuli (eg, lipopolysaccharides) have been shown to increase PDGF secretion from macrophages, aggravating aberrant angiogenesis.[99] Beyond inflammation and angiogenesis, adipose tissue remodeling during obesity is frequently accompanied by fibrosis, characterized by excessive extracellular matrix (ECM) deposition, particularly collagens. Adipose tissue macrophages (ATMs) play a central role in this process by interacting with fibroblasts and promoting their differentiation into ECM-producing myofibroblasts.[100] Importantly, crosstalk between M1-like macrophages and mast cells amplifies this fibrotic response by accelerating adipocyte death and the release of damage-associated molecular patterns (DAMPs) and free fatty acids (FFAs). These signals activate the NF-κB pathway, upregulating CCL2, TNF-α, IL-6, and other cytokines, which establish a positive feedback loop that perpetuates macrophage recruitment, M1 polarization, and chronic systemic inflammation.[101]

These findings underscore the central involvement of immune cells, particularly macrophages, in orchestrating the inflammatory, angiogenic, and fibrotic remodeling of obese WAT, ultimately linking local immune dysregulation to systemic metabolic dysfunction.[102] Given this central role of inflammation and immune imbalance in obesity progression, innovative delivery strategies such as MNs-based systems offer unique opportunities to locally modulate the adipose tissue microenvironment, rebalance M1/M2 macrophage polarization, and attenuate pro-inflammatory cytokine release, thus providing a promising avenue for obesity therapy. A representative example is the HORN-MN system, previously described as a fast-dissolving hyaluronic acid MNs loaded with oleanolic acid–rosiglitazone nanoparticles (Figure 5).[74] Beyond its weight-reducing efficacy, HORN-MN exerted a profound immunomodulatory effect on obese adipose tissue. Treatment significantly lowered the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, restoring them to near-normal levels, while simultaneously promoting adipocyte browning. This dual regulation of inflammation and adipose remodeling contributed to a remarkable 17% reduction in body weight, highlighting the therapeutic promise of MN-based strategies in reshaping the inflammatory microenvironment during obesity management.

In summary, the chronic low-grade inflammation and immune dysregulation within obese adipose tissue, characterized by M1 macrophage polarization and elevated pro-inflammatory cytokines such as TNF-α and IL-6, play a central role in adipose dysfunction and metabolic complications.[103] Targeting this pathological microenvironment not only alleviates inflammation but also restores adipose plasticity, thereby enhancing therapeutic outcomes. Emerging MNs-based delivery systems, provide a promising strategy to directly modulate the inflammatory milieu while promoting adipocyte browning, opening new avenues for effective and patient-friendly obesity management.

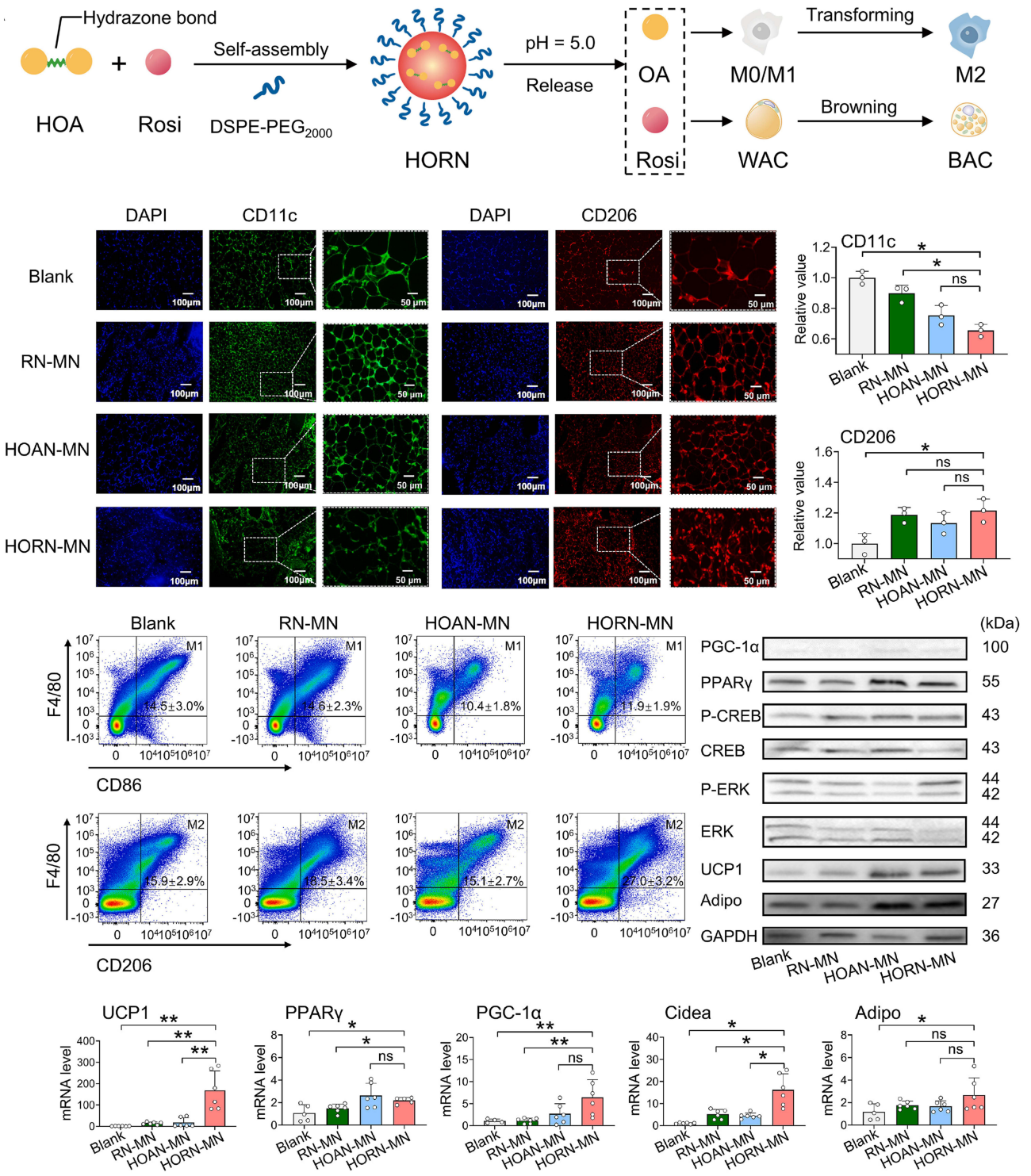

Figure 5 Engineering and mechanism of the HORN-MN patch. Design of HORN nanoparticles: hydrazone-bonded oleic acid (HOA) and rosiglitazone (Rosi) were dissolved in a mixture of tetrahydrofuran, acetone, and ethanol, followed by self-assembly with DSPE-PEG2000. Under acidic conditions, HORN disassembles, releasing Rosi and OA via hydrolysis of the hydrazone bond. OA promotes M0 macrophage remodeling, while Rosi facilitates WAC browning. Transcriptomic analysis revealed that HORN treatment significantly modulates adipose-related genes, regulates the inflammatory microenvironment, and enhances adipocyte browning. DEG, differentially expressed genes. Significance is denoted as ns $p>0.05$. *$p < 0.05$. **$p < 0.01$. Reproduced with permission.[74] Copyright 2024, Elsevier.

Gene Therapy in Obesity Treatment

Recent advances in gene therapy, driven by recombinant adeno-associated viruses (rAAV), synthetic vectors, RNA interference (RNAi), and CRISPR/Cas9 technology, have opened promising avenues for obesity management.[104] Unlike

conventional pharmacological interventions that primarily modulate downstream pathways, gene therapy directly targets the molecular determinants of energy balance, food intake, and lipid storage. Genetic mutations that alter appetite regulation or energy expenditure are closely linked to obesity, underscoring the therapeutic potential of interventions at the genetic level.[105]

Mechanistically, gene therapy strategies for obesity aim either to suppress lipogenesis or to enhance energy expenditure. For instance, overexpression of protective factors such as brain-derived neurotrophic factor (BDNF), irisin, and fibroblast growth factor (FGF) in animal models has been shown to reduce fat mass, while silencing lipogenic genes prevents triglyceride overaccumulation.[104] CRISPR/Cas9-based editing offers precise in situ repair of obesity-associated mutations while preserving normal regulatory elements, whereas RNAi-based approaches, including small interfering RNAs (siRNAs) or microRNA mimics, can silence key metabolic genes and improve glucose and lipid homeostasis.[106]

Short hairpin RNA (shRNA) therapy represents another potent tool for targeted gene silencing. Once translocated into the nucleus, shRNA is processed by DICER into siRNAs, which are incorporated into the RNA-induced silencing complex (RISC) to degrade complementary messenger RNAs. This mechanism enables inhibition of lipogenic targets such as fatty acid–binding proteins (FABP4/5), thereby reducing lipid storage and restoring metabolic balance.[107] A notable example is the development of a dissolvable hyaluronic acid–based self-locking MN (LMN) patch for delivering self-assembled oligopeptoplex (SA-OP) carrying shRNA constructs (Figure 6A).[75] This minimally invasive platform overcomes traditional delivery challenges, including genetic material instability and injection-associated discomfort. In vivo studies in diet-induced obese mice demonstrated potent adipose tissue gene silencing, a 21.9% reduction in body weight, and improvements in insulin resistance, inflammation, and hepatic steatosis within six weeks.

Similarly, CRISPR-based systems have shown strong therapeutic potential. For example, targeted delivery of CRISPR interference (CRISPRi) against Fabp4 to white adipocytes reduced body weight, ameliorated inflammation, and improved hepatic steatosis and insulin sensitivity in murine models.[108] More recently, a MN-enabled sono-gene therapy platform has been developed that combines methoxy polyethylene glycol–polyethyleneimine (mPEG-PEI)–modified metal–organic framework (MOF) sonosensitizers with a CRISPR activation (CRISPRa) system targeting UCP1 (Figure 6B).[76] This dual strategy achieved both the elimination of redundant white adipocytes via sonodynamic therapy and the promotion of adipocyte browning through CRISPRa-mediated UCP1 upregulation. In obese mice, this approach significantly improved glucose tolerance and insulin sensitivity, produced substantial weight loss, and effectively prevented weight rebound.

In summary, gene therapy offers a transformative approach to obesity treatment by directly modulating the molecular pathways governing energy homeostasis. The integration of minimally invasive delivery technologies, particularly MNs, has further expanded the feasibility of translating these strategies into clinical settings by enhancing safety, patient compliance, and therapeutic precision. While long-term efficacy and safety require further validation, the convergence of advanced gene-editing tools and innovative delivery platforms holds considerable promise for establishing next-generation therapies against obesity and its metabolic complications.

MNs Combined with PTT for Obesity Treatment

Photothermal therapy (PTT) is a non-invasive approach that converts light energy into localized heat, inducing apoptosis in target cells with high spatiotemporal precision and minimal side effects. Initially developed for tumor ablation, PTT has recently been applied to obesity treatment due to its ability to modulate WAT metabolism.[109] Localized hyperthermia can promote WAT browning, enhance mitochondrial activity, accelerate lipid catabolism, and thereby reduce fat mass while improving metabolic parameters.

Conventional PTT strategies for obesity commonly employ photothermal agent-loaded injectable hydrogels, yet these approaches face several limitations. Transdermal delivery may cause damage to the skin and surrounding tissues; the hydrogels themselves must satisfy stringent physicochemical requirements, such as high temperature sensitivity, adequate water solubility, and biodegradability; and repeated subcutaneous injections can lead to adverse effects including pain, inflammation, fat atrophy, and the formation of subcutaneous nodules.[110,111] Integrating MNs platforms with PTT offers a promising solution. MNs can deliver photothermal agents directly into the dermis or subcutaneous WAT with minimal invasiveness, avoiding large-volume injections and reducing local tissue damage. The combination of MN-mediated

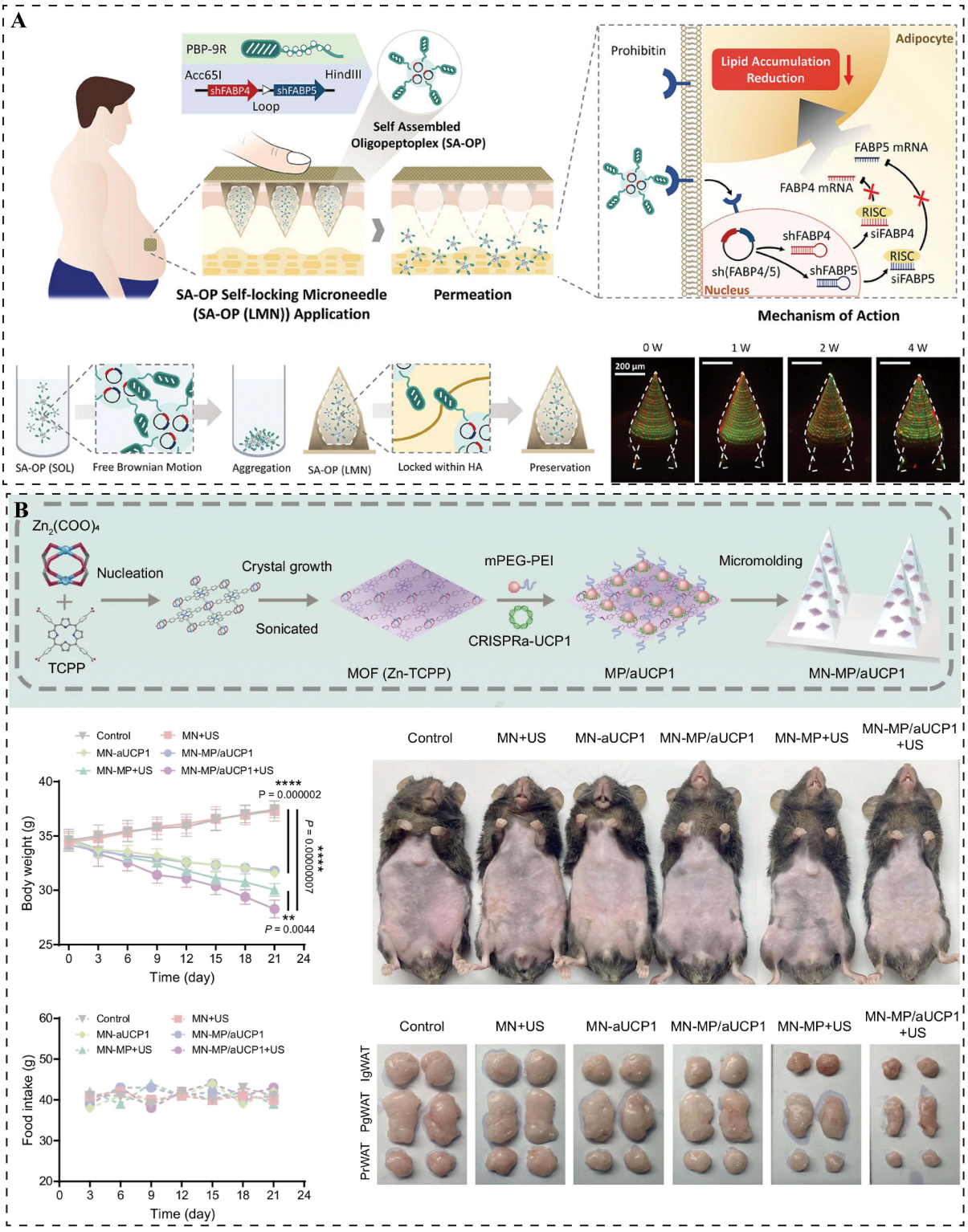

Figure 6 (**A**) Application, fabrication, and mechanism of action of SA-OP LMN patches. Schematic illustration of SA-OP LMN fabrication and application. SA-OPs are formed through electrostatic interaction between the therapeutic gene sh(FABP4/5) and the cell-penetrating peptide PBP9R, and subsequently incorporated into a HA matrix to produce LMN patches. Mechanism of action in obese adipocytes. After patch dissolution and release, SA-OPs enter the systemic circulation and selectively target prohibitin-overexpressing white adipocytes. Following endocytosis, PBP9R facilitates endosomal escape and nuclear delivery of sh(FABP4/5), which is processed by Dicer into siRNA duplexes. These duplexes associate with RISC to silence FABP4 and FABP5 mRNAs, thereby reducing lipid accumulation in adipocytes. Reproduced with permission.[75] Copyright 2024, Wiley-VCH GmbH. (**B**) Preparation and therapeutic application of the MN-MP/aUCP1 patch in a spatiotemporally controllable sono-gene therapy platform for obesity. (a) Schematic illustration of the synthesis process of the MN-MP/aUCP1 patch and its anti-obesity treatment under US irradiation, highlighting long-term therapeutic benefits. Significance is denoted as **p < 0.01. ****p < 0.0001. Reproduced with permission.[76] Copyright 2025, Springer Nature.

delivery and localized photothermal heating enables precise induction of WAT browning, enhanced lipid metabolism, and targeted reduction of adipocyte size while minimizing systemic side effects. For example, Li et al developed a Fe_3O_4 nanoparticle–encapsulated MN patch (Fe_3O_4@MNP) combined with near-infrared (NIR) irradiation to perform localized photothermal therapy (LPTT) in high-fat diet–induced obese mice (Figure 7A).[77] This localized hyperthermia promoted WAT browning and thermogenesis via activation of the HSF1–PGC1α transcriptional axis and upregulation of HSP72. After four weeks of treatment, mice in the Fe_3O_4@MNP + NIR group exhibited a 19% reduction in body weight compared to controls, along with improvements in glucose tolerance, lipid metabolism, and alleviation of nonalcoholic fatty liver disease (NAFLD). The combination of PTT and MNs has also been shown to enhance UCP-1 expression within adipose tissue. A representative example involves self-assembled stearic acid–modified chitosan oligosaccharide (COA) nanoparticles delivered via an effervescent MN patch, co-loaded with the photothermal agent indocyanine green (Figure 7B).[68] The effervescent MNs facilitate efficient skin penetration and precise intradermal delivery of nanoparticles to subcutaneous adipose tissue. Upon NIR irradiation, localized heat generated by PTT synergizes with COA-mediated autolysosomal degradation of lipid droplets, inducing white adipocyte browning and reducing lipid accumulation. In diet-induced obese mice, this combined therapy significantly decreased body weight and WAT mass over four weeks, without affecting food intake, and improved glucose metabolism and insulin sensitivity.

Overall, MN-mediated PTT represents a minimally invasive, precise, and highly effective strategy for promoting WAT browning and improving metabolic health, offering a promising alternative to conventional obesity therapies.

MNs Combined with Iontophoresis for Obesity Treatment

Iontophoresis (INT) is a non-invasive transdermal drug delivery technique that uses a low-intensity electric current (typically 0.1–1.0 mA/cm^2) to facilitate the transport of charged molecules across the skin. This process relies on generating a potential gradient that drives ionic drugs through electrostatic interactions.[112] Two primary mechanisms are involved: electrokinetic migration, which directs ions toward oppositely charged electrodes, and electroosmosis, which promotes the bulk movement of water molecules from the anode to the cathode. The efficiency of INT depends on multiple factors, including drug concentration, molecular charge, physicochemical properties, solubility, molecular size, as well as the integrity of the skin barrier, stratum corneum thickness, and local blood flow.[113] INT thus offers a promising method to enhance transdermal drug penetration with minimal adverse effects, providing an attractive alternative to conventional injections.

Integrating INT with MNs further improves transdermal delivery efficiency. In this approach, MNs create microchannels through the stratum corneum, while INT actively drives charged drugs deeper into subcutaneous tissues via electromotive force. This synergistic strategy enhances skin permeation, enables precise local delivery, and broadens the range of therapeutics suitable for transdermal administration.[114] For example, Vemulapalli et al reported a 25-fold increase in methotrexate delivery in vivo when MNs and INT were combined compared to either technique alone.[115] Likewise, Li et al developed an iontophoresis-driven porous MN array that achieved up to 99% skin penetration and significantly improved delivery of insulin nanovesicles (5.8 kDa) relative to MNs or INT alone.[116] In the context of obesity treatment, the combination of MNs and INT can effectively enhance the delivery of anti-obesity agents, such as lipolytic drugs, gene therapy vectors, or browning-inducing compounds, directly into subcutaneous white adipose tissue.[117] By leveraging both MN-created microchannels and INT-driven electromotive transport, therapeutic agents can efficiently reach adipocytes, promoting lipid metabolism, inducing white adipocyte browning, and improving systemic metabolic profiles.

In summary, the MN-INT combination provides a precise, minimally invasive, and highly effective strategy for enhancing transdermal delivery of anti-obesity therapeutics, offering potential for improved metabolic outcomes with reduced patient discomfort.

Challenges and Perspectives

MNs-based therapeutics for obesity treatment offer several distinct advantages. First, MNs enable targeted delivery to subcutaneous adipose tissue, minimizing systemic exposure and reducing off-target toxicity.[17] Second, as a non-injection approach, MNs improve patient compliance, particularly for chronic conditions that require repeated administration. Third, MNs can be designed for sustained or controlled release, making them suitable for long-term management of obesity and

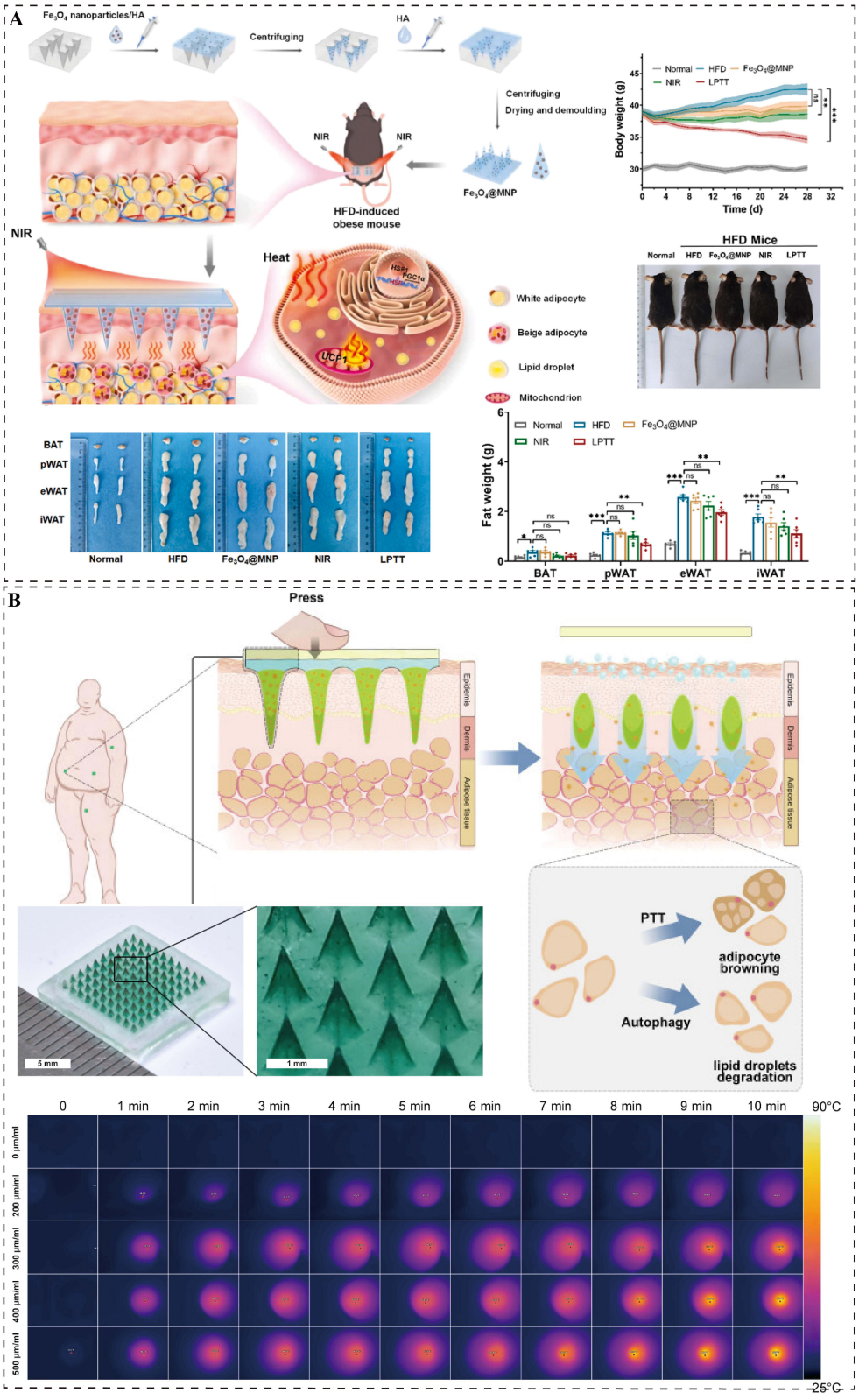

Figure 7 (**A**) Schematic illustration of Fe_3O_4@MNP-based LPTT for promoting WAT browning in HFD-induced obesity and evaluation of the anti-obesity efficacy of Fe_3O_4@MNP-based LPTT in HFD-induced obese mice. Significance is denoted as ns $p>0.05$. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Reproduced with permission.[77] Copyright 2025, Elsevier. (**B**) Schematic illustration of the proposed multilayered MN system composed of a backing layer, an effervescent layer, and needle tips. Upon insertion, the effervescent layer reacts with interstitial fluid to generate carbon dioxide, propelling the MN tips deep into the dermal layer under the support of the backing layer. Co-loaded indocyanine green (ICG) and COA nanoparticles are subsequently released and distributed within subcutaneous adipose tissue. Under localized PTT, ICG mediates the conversion of white adipocytes into beige adipocytes with enhanced energy metabolism, while COA nanoparticles specifically target adipocytes and promote lipid droplet degradation through the autolysosomal pathway. Reproduced with permission.[68] Copyright 2025, American Chemical Society.

metabolic disorders.[79] Finally, MNs are versatile platforms capable of delivering a broad spectrum of therapeutics, including peptides, nucleic acids, and other macromolecular drugs, which are often challenging to administer via conventional routes.

Despite these advantages, several challenges remain for MN-mediated obesity therapies. Drug loading capacity is inherently limited by the physical dimensions of MNs, which may restrict therapeutic dosing for certain agents.[118] Moreover, variability in skin penetration arising from differences in skin thickness, elasticity, and hydration among individuals can lead to inconsistent drug delivery efficiency and therapeutic outcomes.[119] Factors such as skin thickness variation across body sites (eg, abdomen vs arm), age, ethnicity, and individual physiological differences, particularly in patients with obesity, can further exacerbate this variability and impact the reproducibility of treatment outcomes. Skin barrier properties and local tissue heterogeneity can affect the penetration, stability, and bioavailability of delivered therapeutics.[120] Clinical evidence supporting the efficacy and safety of MN-based obesity interventions is still relatively sparse, with most studies limited to preclinical animal models. In addition, scaling up microneedle fabrication from laboratory prototypes to Good Manufacturing Practice (GMP) standards represents a major translational hurdle. Achieving consistent, high-volume production while maintaining product quality and reproducibility remains challenging. The complex and time-consuming nature of mold preparation, polymer curing, and drying processes, particularly for dissolving MNs, further complicates mass production. Ensuring the long-term mechanical stability, performance, and safety of MN under clinical manufacturing conditions also demands stringent process optimization and validation. Finally, the potential for local skin reactions, including irritation, erythema, or post-removal hyperpigmentation, especially with chronic or repeated MN applications, warrants careful evaluation. These local adverse effects may compromise patient comfort, compliance, and acceptance in long-term obesity management, underscoring the importance of using biocompatible materials and optimizing application protocols to minimize irritation.

When interpreting preclinical studies, it is important to recognize the anatomical and physiological differences between murine and human skin. Human skin is generally much thicker than murine skin, particularly in the stratum corneum and dermis, which can reduce MNs penetration efficiency and alter drug diffusion profiles. Additionally, human skin has a lower density of hair follicles and sebaceous glands, which can influence local absorption, microchannel formation, and distribution of delivered therapeutics. Variations in skin elasticity, hydration, and collagen content also contribute to differences in mechanical resistance compared to murine models, potentially affecting MNs insertion and reproducibility. Adipose tissue biology also differs substantially between species. Humans exhibit a more heterogeneous distribution of subcutaneous and visceral fat depots, with larger adipocyte sizes and distinct metabolic activity compared to mice. The proportion of brown versus white adipose tissue, thermogenic capacity, and responsiveness to browning agents may vary, influencing the translational efficacy of interventions designed to induce adipocyte browning or modulate lipid metabolism. These species-specific differences underscore the need for careful optimization of MNs design, dosing strategies, and therapeutic regimens when translating findings from murine models to humans.

Looking ahead, the clinical translation of MN-based obesity therapy holds great promise but requires continued interdisciplinary innovation. In the near term, integrating MN systems with advanced nanomedicine platforms could enhance drug loading efficiency, improve formulation stability, and achieve spatiotemporally controlled release to adipose tissues.[121] AI-assisted MN design may further support personalized treatment strategies by optimizing penetration depth, dosing regimens, and patient adherence according to individual metabolic and skin characteristics. The development of multifunctional, smart MN patches capable of monitoring physiological parameters and providing real-time, feedback-controlled drug release could revolutionize long-term obesity management. To bridge the gap between preclinical success and real-world application, future research should focus on large-scale clinical validation, long-term safety assessment, and regulatory standardization. Ultimately, these efforts will pave the way for MN-based platforms to become practical, patient-friendly solutions for obesity and related metabolic disorders.In summary, MN-based delivery systems hold considerable promise for obesity therapy, combining targeted, patient-friendly delivery with the potential for personalized, multifunctional treatment, while ongoing innovations and clinical evaluation are needed to fully realize their therapeutic potential.

Conclusion

MN-based delivery offers a novel perspective for obesity treatment, enabling precise, minimally invasive targeting of subcutaneous adipose tissue. Recent studies demonstrate that multi-target and multi-mechanism intervention strategies, ranging from gene therapy and peptide delivery to photothermal and iontophoretic approaches, show promising efficacy in

modulating adipose tissue metabolism, inducing white adipocyte browning, and improving systemic metabolic profiles. With ongoing advances in delivery technologies, integration with nanomedicine, and the progression of translational research, MNs could provide a new approach in anti-obesity therapy, offering patient-friendly, targeted, and potentially effective treatment options for the management of obesity and related metabolic disorders, pending robust clinical validation.

Acknowledgments

The authors gratefully acknowledge the financial support for this research from the Natural Science Foundation of Shanghai (25ZR1402163).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ladher N, Hinton R, Veitch E. Challenges of obesity and type 2 diabetes require more attention to food environment. *BMJ*. 2023;383:2269. doi:10.1136/bmj.p2269
2. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. *Circulation Res*. 2020;126(11):1477–1500. doi:10.1161/CIRCRESAHA.120.316101
3. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metab Clin Exp*. 2019;92:82–97. doi:10.1016/j.metabol.2018.11.014
4. Hopkins BD, Goncalves MD, Cantley LC. Obesity and Cancer Mechanisms: cancer Metabolism. *JCO*. 2016;34(35):4277–4283. doi:10.1200/JCO.2016.67.9712
5. Ruban A, Stoenchev K, Ashrafian H, Teare J. Current treatments for obesity. *Clin Med*. 2019;19(3):205–212. doi:10.7861/clinmedicine.19-3-205
6. Subramaniyan V, Hanim YU. Role of pancreatic lipase inhibition in obesity treatment: mechanisms and challenges towards current insights and future directions. *Int J Obesity*. 2025;49(3):492–506. doi:10.1038/s41366-025-01729-1
7. Wang JY, Wang QW, Yang XY, et al. GLP−1 receptor agonists for the treatment of obesity: role as a promising approach. *Front Endocrinol*. 2023;14:1085799. doi:10.3389/fendo.2023.1085799
8. Grunvald E, Shah R, Hernaez R, et al. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. *Gastroenterology*. 2022;163(5):1198–1225. doi:10.1053/j.gastro.2022.08.045
9. Courcoulas AP, Daigle CR, Arterburn DE. Long term outcomes of metabolic/bariatric surgery in adults. *BMJ*. 2023;383. doi:10.1136/bmj-2022-071027
10. Tian Y, Xia L, Song X, Chen Y. Dissolving Microneedles as In Situ Chemical Reaction Chambers: from Design Strategies to Versatile Biomedical Applications. *Adv Funct Mater*. 2025;35(23):2422274. doi:10.1002/adfm.202422274
11. Cao Y, Kim D, Koh SS, et al. Nanofabrication of silk microneedles for high-throughput micronutrient delivery and continuous sap monitoring in plants. *Nature Nanotechnol*. 2025;2025:2. doi:10.1038/s41565-025-01923-2
12. Wu Y, Vora LK, Wang Y, et al. Long-acting nanoparticle-loaded bilayer microneedles for protein delivery to the posterior segment of the eye. *Eur J Pharm Biopharm*. 2021;165:306–318. doi:10.1016/j.ejpb.2021.05.022
13. Tobos CI, Woodrow KA. Dissolving microneedles for nucleic acid delivery: a systematic search, review, and data synthesis. *Acta Biomater*. 2025;200:115–131. doi:10.1016/j.actbio.2025.05.025
14. Li Y, Chen Q, Wang T, et al. Advances in microneedle-based drug delivery system for metabolic diseases: structural considerations, design strategies, and future perspectives. *J Nanobiotechnol*. 2025;23(1):350. doi:10.1186/s12951-025-03432-9
15. Tian Y, Lee J, van der Maaden K, et al. Intradermal Administration of Influenza Vaccine with Trehalose and Pullulan-Based Dissolving Microneedle Arrays. *J Pharmaceut Sci*. 2022;111(4):1070–1080. doi:10.1016/j.xphs.2022.01.033
16. Zhang Y, Liu Q, Yu J, et al. Locally Induced Adipose Tissue Browning by Microneedle Patch for Obesity Treatment. *ACS Nano*. 2017;11(9):9223–9230. doi:10.1021/acsnano.7b04348
17. Chilamakuri SN, M N, Thalla M, et al. Role of Microneedles for Improved Treatment of Obesity: progress and Challenges. *Mol Pharm*. 2025;22(5):2350–2371. doi:10.1021/acs.molpharmaceut.4c01115
18. Abdel-Kadar M. Percutaneous Electrical Neurostimulation (PENS) of Dermatome T6 with an Ambulatory Self-applied Patch vs PENS of Dermatome T6 with Conventional Procedure: effect on Appetite and Weight Loss in Moderately Obese Patients. *Obesity Surgery*. 2016;26(12):2899–2905. doi:10.1007/s11695-016-2214-0
19. Zhang Y, Xu Y, Kong H, et al. Microneedle system for tissue engineering and regenerative medicine. *Exploration*. 2023;3(1):20210170. doi:10.1002/EXP.20210170

20. Cahill EM, Keaveney S, Stuettgen V, et al. Metallic microneedles with interconnected porosity: a scalable platform for biosensing and drug delivery. *Acta Biomater*. 2018;80:401–411. doi:10.1016/j.actbio.2018.09.007
21. Puri A, Nguyen HX, Tijani AO, Banga AK. Characterization of Microneedles and Microchannels for Enhanced Transdermal Drug Delivery. *Therapeutic Delivery*. 2021;12(1):77–103. doi:10.4155/tde-2020-0096
22. Li H, Peng Z, Song Y, et al. Study of the permeation-promoting effect and mechanism of solid microneedles on different properties of drugs. *Drug Delivery*. 2023;30(1):2165737. doi:10.1080/10717544.2023.2165737
23. Caudill CL, Perry JL, Tian S, Luft JC, DeSimone JM. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. *J Control Release*. 2018;284:122–132. doi:10.1016/j.jconrel.2018.05.042
24. Ingrole RSJ, Gill HS. Microneedle Coating Methods: a Review with a Perspective. *J Pharmacol Exp Ther*. 2019;370(3):555–569. doi:10.1124/jpet.119.258707
25. Sausse Lhernould M, Delchambre A. Innovative design of hollow polymeric microneedles for transdermal drug delivery. *Microsystem Technol*. 2011;17(10):1675. doi:10.1007/s00542-011-1355-2
26. Avcil M, Çelik A. Microneedles in Drug Delivery: progress and Challenges. *Micromachines*. 2021;12(11). doi:10.3390/mi12111321
27. Tian Y, Jing H, Wang Q, Hu S, Wu Z, Duan Y. Dissolving microneedles-based programmed delivery system for enhanced chemo-immunotherapy of melanoma. *J Control Release*. 2023;360:630–646. doi:10.1016/j.jconrel.2023.07.002
28. Gopan G, Jose J, Khot KB, Bandiwadekar A, Deshpande NS. Hyaluronic acid-based hesperidin nanostructured lipid carriers loaded dissolving microneedles: a localized delivery approach loaded for the management of obesity. *Int J Biol Macromol*. 2025;305:140948. doi:10.1016/j.ijbiomac.2025.140948
29. Ding YW, Li Y, Zhang ZW, Dao JW, Wei DX. Hydrogel forming microneedles loaded with VEGF and Ritlecitinib/polyhydroxyalkanoates nanoparticles for mini-invasive androgenetic alopecia treatment. *Bioact Mater*. 2024;38:95–108. doi:10.1016/j.bioactmat.2024.04.020
30. Leng F, Zheng M, Xu C. 3D-printed microneedles with open groove channels for liquid extraction. *Exploration*. 2021;1(3):20210109. doi:10.1002/EXP.20210109
31. Suriyaamporn P, Dechsri K, Charoenying T, et al. Multiple strategies approach: a novel crosslinked hydrogel forming chitosan-based microneedles chemowrap patch loaded with 5-fluorouracil liposomes for chronic wound cancer treatment. *Int J Biol Macromol*. 2024;279:134973. doi:10.1016/j.ijbiomac.2024.134973
32. Ali M, Namjoshi S, Benson HAE, Mohammed Y, Kumeria T. Dissolvable polymer microneedles for drug delivery and diagnostics. *J Control Release*. 2022;347:561–589. doi:10.1016/j.jconrel.2022.04.043
33. Zhang Y, Jiang G, Yu W, Liu D, Xu B. Microneedles fabricated from alginate and maltose for transdermal delivery of insulin on diabetic rats. *Mater Sci Eng C*. 2018;85:18–26. doi:10.1016/j.msec.2017.12.006
34. Aung NN, Ngawhirunpat T, Rojanarata T, Patrojanasophon P, Opanasopit P, Pamornpathomkul B. HPMC/PVP Dissolving Microneedles: a Promising Delivery Platform to Promote Trans-Epidermal Delivery of Alpha-Arbutin for Skin Lightening. *AAPS Pharm Sci Tech*. 2019;21(1):25. doi:10.1208/s12249-019-1599-1
35. Silva ACQ, Pereira B, Lameirinhas NS, et al. Dissolvable Carboxymethylcellulose Microneedles for Noninvasive and Rapid Administration of Diclofenac Sodium. *Macromol biosci*. 2023;23(1):2200323. doi:10.1002/mabi.202200323
36. Sartawi Z, Blackshields C, Faisal W. Dissolving microneedles: applications and growing therapeutic potential. *J Control Release*. 2022;348:186–205. doi:10.1016/j.jconrel.2022.05.045
37. Park SY, Lee HU, Lee YC, et al. Wound healing potential of antibacterial microneedles loaded with green tea extracts. *Mater Sci Eng C*. 2014;42:757–762. doi:10.1016/j.msec.2014.06.021
38. Saha I, Rai VK. Hyaluronic acid based microneedle array: recent applications in drug delivery and cosmetology. *Carbohydr Polym*. 2021;267:118168. doi:10.1016/j.carbpol.2021.118168
39. Huang C, Gou K, Yue X, et al. A novel hyaluronic acid-based dissolving microneedle patch loaded with ginsenoside Rg3 liposome for effectively alleviate psoriasis. *Mater Des*. 2022;224:111363. doi:10.1016/j.matdes.2022.111363
40. Gorantla S, Dabholkar N, Sharma S, Rapalli VK, Alexander A, Singhvi G. Chitosan-based microneedles as a potential platform for drug delivery through the skin: trends and regulatory aspects. *Int J Biol Macromol*. 2021;184:438–453. doi:10.1016/j.ijbiomac.2021.06.059
41. Lu H, Wang J, Li J, Gao B, He B. Advanced Silk Fibroin Biomaterials-Based Microneedles for Healthcare. *Macromol biosci*. 2023;23(11):2300141. doi:10.1002/mabi.202300141
42. Shu Y, Qi Y, Zou Y, et al. A gelatin microneedles featuring antibacterial and reactive oxygen species scavenging properties for treating Vibrio vulnificus-infected wounds. *Int J Biol Macromol*. 2025;309:142640. doi:10.1016/j.ijbiomac.2025.142640
43. Ulloa Rojas JE, de Oliveira VL, de Araujo DR, et al. Silk Fibroin/Poly(vinyl Alcohol) Microneedles as Carriers for the Delivery of Singlet Oxygen Photosensitizers. *ACS Biomater Sci Eng*. 2022;8(1):128–139. doi:10.1021/acsbiomaterials.1c00913
44. Marin E, Briceño MI, Caballero-George C. Critical evaluation of biodegradable polymers used in nanodrugs. *Int J Nanomed*. 2013;8(1):3071–3091. doi:10.2147/IJN.S47186
45. Wang M, Hu L, Xu C. Recent advances in the design of polymeric microneedles for transdermal drug delivery and biosensing. *Lab Chip*. 2017;17(8):1373–1387. doi:10.1039/C7LC00016B
46. Malek-Khatabi A, Sadat Razavi M, Abdollahi A, et al. Recent progress in PLGA-based microneedle-mediated transdermal drug and vaccine delivery. *Biomater Sci*. 2023;11(16):5390–5409. doi:10.1039/D3BM00795B
47. Donnelly RF, Singh TRR, Garland MJ, et al. Hydrogel-Forming Microneedle Arrays for Enhanced Transdermal Drug Delivery. *Adv Funct Mater*. 2012;22(23):4879–4890. doi:10.1002/adfm.201200864
48. Chen W, Wang C, Yan L, et al. Improved polyvinylpyrrolidone microneedle arrays with non-stoichiometric cyclodextrin. *J Mater Chem B*. 2014;2(12):1699–1705. doi:10.1039/C3TB21698E
49. Yang S, Wu F, Liu J, et al. Phase-Transition Microneedle Patches for Efficient and Accurate Transdermal Delivery of Insulin. *Adv Funct Mater*. 2015;25(29):4633–4641. doi:10.1002/adfm.201500554
50. Saepang K, Buranrat B, Pitaksuteepong T, Boontha S. Effect of polyvinyl alcohol concentrations on the characteristics and in vitro skin permeation of rhein-loaded dissolving microneedle patches. *J Drug Delivery Sci Technol*. 2025;108:106955. doi:10.1016/j.jddst.2025.106955
51. Vecchione R, Coppola S, Esposito E, et al. Electro-Drawn Drug-Loaded Biodegradable Polymer Microneedles as a Viable Route to Hypodermic Injection. *Adv Funct Mater*. 2014;24(23):3515–3523. doi:10.1002/adfm.201303679

52. Koyani RD. Synthetic polymers for microneedle synthesis: from then to now. *J Drug Delivery Sci Technol*. 2020;60:102071. doi:10.1016/j.jddst.2020.102071
53. Jiang X, Zhang W, Terry R, Li W. The progress of fabrication designs of polymeric microneedles and related biomedical applications. *BMEMat*. 2023;1(4):e12044. doi:10.1002/bmm2.12044
54. Sargioti N, Levingstone TJ, O'Cearbhaill ED, McCarthy HO, Dunne NJ. Metallic Microneedles for Transdermal Drug Delivery: applications, Fabrication Techniques and the Effect of Geometrical Characteristics. *Bioengineering*. 2023;10(1). doi:10.3390/bioengineering10010024
55. Mohd Noor SN, Zainal Abidin HE, Ooi PC, Hamzah AA. Chapter 5 - Silicon microneedles for drug delivery. In: Kesharwani P editor. *Design and Applications of Microneedles in Drug Delivery and Therapeutics*. Academic Press; 2024:147–173. doi:10.1016/B978-0-443-13881-2.00007-2
56. Yuan Z, Zhang H, Hu W, et al. State-of-the-art Review of Metallic Microneedles: structure, Fabrication, and Application. *Chin J Mech Eng*. 2025;38(1):21. doi:10.1186/s10033-025-01188-9
57. Kim J, Jeong J, Jo JK, So H. Hollow microneedles as a flexible dosing control solution for transdermal drug delivery. *Mater Today Bio*. 2025;32:101754. doi:10.1016/j.mtbio.2025.101754
58. Ji H, Wang M, Wang Y, et al. Skin-integrated, biocompatible, and stretchable silicon microneedle electrode for long-term EMG monitoring in motion scenario. *NPJ Flexible Electron*. 2023;7(1):46. doi:10.1038/s41528-023-00279-8
59. Downs AM, Bolotsky A, Weaver BM, et al. Microneedle electrochemical aptamer-based sensing: real-time small molecule measurements using sensor-embedded, commercially-available stainless steel microneedles. *Biosens Bioelectron*. 2023;236:115408. doi:10.1016/j.bios.2023.115408
60. Parker ER, Rao MP, Turner KL, Meinhart CD, MacDonald NC. Bulk Micromachined Titanium Microneedles. *J Microelectromech Syst*. 2007;16(2):289–295. doi:10.1109/JMEMS.2007.892909
61. Yang Y, Sun H, Sun X, et al. From mechanism to applications: advanced microneedles for clinical medicine. *Bioact Mater*. 2025;51:1–45. doi:10.1016/j.bioactmat.2025.04.025
62. Sedky M, Ali A, Abdel-Mottaleb M, Serry M. A new rapid-release SMA-activated micropump with incorporated microneedle arrays and polymeric nanoparticles for optimized transdermal drug delivery. *Sensors and Actuat B Chem*. 2024;408:135549. doi:10.1016/j.snb.2024.135549
63. You J, Yang C, Han J, et al. Ultrarapid-Acting Microneedles for Immediate Delivery of Biotherapeutics. *Adv Mater*. 2023;35(45):2304582. doi:10.1002/adma.202304582
64. Vora LK, Sabri AH, Naser Y, et al. Long-acting microneedle formulations. *Adv Drug Delivery Rev*. 2023;201:115055. doi:10.1016/j.addr.2023.115055
65. Ruan H, Long M, Li J, Zhang D, Feng N, Zhang Y. Sustained-Release Hydrogen-Powered Bilateral Microneedles Integrating CD-MOFs for In Situ Treating Allergic Rhinitis. *Adv Healthcare Mater*. 2024;13(22):2400637. doi:10.1002/adhm.202400637
66. Liu R, Li A, Lang Y, et al. Stimuli-responsive polymer microneedles: a rising transdermal drug delivery system and Its applications in biomedical. *J Drug Delivery Sci Technol*. 2023;88:104922. doi:10.1016/j.jddst.2023.104922
67. Makvandi P, Jamaledin R, Chen G, et al. Stimuli-responsive transdermal microneedle patches. *Mater Today*. 2021;47:206–222. doi:10.1016/j.mattod.2021.03.012
68. Luo M, Zhang Y, He S, et al. Effervescent Microneedles for the Codelivery of Chitosan Nanoparticles and Indocyanine Green To Enhance the Treatment of Diet-Induced Obesity in Mice. *ACS Nano*. 2025;19(12):11792–11806. doi:10.1021/acsnano.4c13609
69. Zhu Q, Chen Z, Paul PK, Lu Y, Wu W, Qi J. Oral delivery of proteins and peptides: challenges, status quo and future perspectives. *Acta Pharmaceutica Sinica B*. 2021;11(8):2416–2448. doi:10.1016/j.apsb.2021.04.001
70. Wu P, Zhang T, Zhao D, et al. Microneedle-Enabled Breakthroughs in Nucleic Acid Therapeutics. *Adv Healthcare Mater*. 2025;14(16):2501015. doi:10.1002/adhm.202501015
71. Pan H, Hu W, Zhou C, et al. Microneedle-Mediated Treatment of Obesity. *Pharmaceutics*. 2025;17(2). doi:10.3390/pharmaceutics17020248
72. Li L, Zhou Y, Sun C, et al. Fully integrated wearable microneedle biosensing platform for wide-range and real-time continuous glucose monitoring. *Acta Biomater*. 2024;175:199–213. doi:10.1016/j.actbio.2023.12.044
73. Hu W, Peng T, Huang Y, et al. Hyaluronidase-powered microneedles for significantly enhanced transdermal delivery efficiency. *J Control Release*. 2023;353:380–390. doi:10.1016/j.jconrel.2022.11.046
74. Chen S, Wang J, Sun L, et al. A quick paster type of soluble nanoparticle microneedle patch for the treatment of obesity. *Biomaterials*. 2024;311:122687. doi:10.1016/j.biomaterials.2024.122687
75. Choi H, Hong J, Seo Y, et al. Self-Assembled Oligopeptoplex-Loaded Dissolving Microneedles for Adipocyte-Targeted Anti-Obesity Gene Therapy. *Adv Mater*. 2024;36(16):2309920. doi:10.1002/adma.202309920
76. Li S, Yu J, Shen Y, et al. Transdermal microneedle-assisted ultrasound-enhanced CRISPRa system to enable sono-gene therapy for obesity. *Nat Commun*. 2025;16(1):1499. doi:10.1038/s41467-025-56755-4
77. Li L, Chen H, Zhang K, et al. Microneedles-based local photothermal therapy promotes browning of white adipose tissue and combats obesity. *Mater Today Bio*. 2025;34:102167. doi:10.1016/j.mtbio.2025.102167
78. Hu T, Zhang Z, Xu C. Transdermal delivery of dextran using conductive microneedles assisted by iontophoresis. *J Mater Chem B*. 2022;10(39):8075–8081. doi:10.1039/D2TB01049F
79. Abbasi M, Fan Z, Dawson JA, Wang S. Transdermal Delivery of Metformin Using Dissolving Microneedles and Iontophoresis Patches for Browning Subcutaneous Adipose Tissue. *Pharmaceutics*. 2022;14(4):879. doi:10.3390/pharmaceutics14040879
80. Luo L, Liu M. Adipose tissue in control of metabolism. *J Endocrinol*. 2016;231(3):R77–R99. doi:10.1530/JOE-16-0211
81. Au-Yong ITH, Thorn N, Ganatra R, Perkins AC, Symonds ME. Brown Adipose Tissue and Seasonal Variation in Humans. *Diabetes*. 2009;58(11):2583–2587. doi:10.2337/db09-0833
82. Xiao-Bing C, Shi-You C. White adipose tissue browning and obesity. *J Biomed Res*. 2017;31(1):1–2. doi:10.7555/JBR.31.20160101
83. Ziqubu K, Dludla PV, Mthembu SXH, et al. An insight into brown/beige adipose tissue whitening, a metabolic complication of obesity with the multifactorial origin. *Front Endocrinol*. 2023;14:1114767. doi:10.3389/fendo.2023.1114767
84. Fedorenko A, Lishko PV, Kirichok Y. Mechanism of Fatty-Acid-Dependent UCP1 Uncoupling in Brown Fat Mitochondria. *Cell*. 2012;151(2):400–413. doi:10.1016/j.cell.2012.09.010

85. Wang H, Liu L, Lin JZ, Aprahamian TR, Farmer SR. Browning of White Adipose Tissue with Roscovitine Induces a Distinct Population of UCP1+ Adipocytes. *Cell Metab*. 2016;24(6):835–847. doi:10.1016/j.cmet.2016.10.005
86. Loft A, Forss I, Siersbæk MS, et al. Browning of human adipocytes requires KLF11 and reprogramming of PPARγ superenhancers. *Genes Dev*. 2015;29(1):7–22. doi:10.1101/gad.250829.114
87. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481(7382):463–468. doi:10.1038/nature10777
88. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging Role of GLP-1 Agonists in Obesity: a Comprehensive Review of Randomised Controlled Trials. *Int J Mol Sci*. 2023;24(13). doi:10.3390/ijms241310449
89. Mozaffarian D, Agarwal M, Aggarwal M, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint Advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society. *Am J Clinl Nutr*. 2025;122(1):344–367. doi:10.1016/j.ajcnut.2025.04.023
90. Knudsen LB. Inventing Liraglutide, a Glucagon-Like Peptide-1 Analogue, for the Treatment of Diabetes and Obesity. *ACS Pharmacol Transl Sci*. 2019;2(6):468–484. doi:10.1021/acsptsci.9b00048
91. Zhao X, Wang M, Wen Z, et al. GLP-1 Receptor Agonists: beyond Their Pancreatic Effects. *Front Endocrinol*. 2021;12:721135. doi:10.3389/fendo.2021.721135
92. Dejgaard TF, Frandsen CS, Kielgast U, et al. Liraglutide enhances insulin secretion and prolongs the remission period in adults with newly diagnosed type 1 diabetes (the NewLira study): a randomized, double-blind, placebo-controlled trial. *Diabetes Obesity Metab*. 2024;26(11):4905–4915. doi:10.1111/dom.15889
93. Seo YG. Side Effects Associated with Liraglutide Treatment for Obesity as Well as Diabetes. *Journal of Obesity & Metabolic Syndrome*. 2021;30(1):12–19. doi:10.7570/jomes20059
94. Rabiei M, Kashanian S, Bahrami G, et al. Dissolving microneedle-assisted long-acting Liraglutide delivery to control type 2 diabetes and obesity. *Eur J Pharm Sci*. 2021;167:106040. doi:10.1016/j.ejps.2021.106040
95. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity*. 2022;55(1):31–55. doi:10.1016/j.immuni.2021.12.013
96. Artemniak-Wojtowicz D, Kucharska A, Pyrżak B. Obesity and chronic inflammation crosslinking. *Cent Eur J Immunol*. 2020;45(4):461–468. doi:10.5114/ceji.2020.103418
97. Thomas D, Apovian C. Macrophage functions in lean and obese adipose tissue. *Metab Clin Exp*. 2017;72:120–143. doi:10.1016/j.metabol.2017.04.005
98. Habanjar O, Diab-Assaf M, Caldefie-Chezet F, Delort L. The Impact of Obesity, Adipose Tissue, and Tumor Microenvironment on Macrophage Polarization and Metastasis. *Biology*. 2022;11(2). doi:10.3390/biology11020339
99. Basu S, Choudhury IN, Lee JYP, Chacko A, Ekberg JAK, St John JA. Macrophages Treated with VEGF and PDGF Exert Paracrine Effects on Olfactory Ensheathing Cell Function. *Cells*. 2022;11(15). doi:10.3390/cells11152408
100. Ruiz-Ojeda FJ, Méndez-Gutiérrez A, Aguilera CM, Plaza-Díaz J. Extracellular Matrix Remodeling of Adipose Tissue in Obesity and Metabolic Diseases. *Int J Mol Sci*. 2019;20(19). doi:10.3390/ijms20194888
101. Elieh Ali Komi D, Shafaghat F, Christian M. Crosstalk Between Mast Cells and Adipocytes in Physiologic and Pathologic Conditions. *Clin Rev Allergy Immunol*. 2020;58(3):388–400. doi:10.1007/s12016-020-08785-7
102. Li J, Guo C, Yang X, et al. Effects of natural products on macrophage immunometabolism: a new frontier in the treatment of metabolic diseases. *Pharmacol Res*. 2025;213:107634. doi:10.1016/j.phrs.2025.107634
103. Zatterale F, Longo M, Naderi J, et al. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Front Physiol*. 2020;10:1. doi:10.3389/fphys.2019.01607
104. Sheikh-Hosseini M, Moarefzadeh M, Alsaedi AA, et al. Innovative gene therapy strategies for tackling obesity. *Egypt J Med Hum Genet*. 2025;26(1):58. doi:10.1186/s43042-025-00686-8
105. Tonin G, Eržen S, Mlinarič Z, et al. The Genetic Blueprint of Obesity: from Pathogenesis to Novel Therapies. *Obesity Rev*. 2025;2025:e13978. doi:10.1111/obr.13978
106. Li T, Yang Y, Qi H, et al. CRISPR/Cas9 therapeutics: progress and prospects. *Signal Transduct Target Ther*. 2023;8(1):36. doi:10.1038/s41392-023-01309-7
107. Gorabi AM, Kiaie N, Aslani S, Jamialahmadi T, Johnston TP, Sahebkar A. Prospects for the potential of RNA interference in the treatment of autoimmune diseases: small interfering RNAs in the spotlight. *J Autoimmun*. 2020;114:102529. doi:10.1016/j.jaut.2020.102529
108. Chung JY, Ain QU, Song Y, Yong SB, Kim YH. Targeted delivery of CRISPR interference system against *Fabp4* to white adipocytes ameliorates obesity, inflammation, hepatic steatosis, and insulin resistance. *Genome Res*. 2019;29(9):1442–1452. doi:10.1101/gr.246900.118
109. Zhang Y, Luo M, Jia Y, et al. Adipocyte-targeted delivery of rosiglitazone with localized photothermal therapy for the treatment of diet-induced obesity in mice. *Acta Biomater*. 2024;181:317–332. doi:10.1016/j.actbio.2024.04.029
110. Liu WS, Chen Z, Lu ZM, et al. Multifunctional hydrogels based on photothermal therapy: a prospective platform for the postoperative management of melanoma. *J Control Release*. 2024;371:406–428. doi:10.1016/j.jconrel.2024.06.001
111. Mu R, Gu G, Xu Y, Xi Y, Wei G. Photo-stimulating dual-network microminiature hydrogels reinforced with silver sulfide nanoparticles for regulated cancer photothermal therapy. *Chem Eng J*. 2025;510:161836. doi:10.1016/j.cej.2025.161836
112. Roustit M, Blaise S, Cracowski JL. Trials and tribulations of skin iontophoresis in therapeutics. *Br J Clin Pharmacol*. 2014;77(1):63–71. doi:10.1111/bcp.12128
113. Delgado-Charro MB. Recent advances on transdermal iontophoretic drug delivery and non-invasive sampling. *J Drug Delivery Sci Technol*. 2009;19(2):75–88. doi:10.1016/S1773-2247(09)50015-9
114. Abbasi M, Heath B. Iontophoresis and electroporation-assisted microneedles: advancements and therapeutic potentials in transdermal drug delivery. *Drug Delivery Transl Res*. 2025;15(6):1962–1984. doi:10.1007/s13346-024-01722-7
115. Vemulapalli V, Yang Y, Friden PM, Banga AK. Synergistic effect of iontophoresis and soluble microneedles for transdermal delivery of methotrexate. *J Pharm Pharmacol*. 2008;60(1):27–33. doi:10.1211/jpp.60.1.0004
116. Li Y, Yang J, Zheng Y, et al. Iontophoresis-driven porous microneedle array patch for active transdermal drug delivery. *Acta Biomater*. 2021;121:349–358. doi:10.1016/j.actbio.2020.12.023

117. Ashour MM, Mabrouk M, Aboelnasr MA, Beherei HH, Tohamy KM, Das DB. Anti-Obesity Drug Delivery Systems: recent Progress and Challenges. *Pharmaceutics*. 2023;15(11). doi:10.3390/pharmaceutics15112635
118. Jindal AB, Bhide AR, Salave S, Rana D, Benival D. Long-acting parenteral drug delivery systems for the treatment of chronic diseases. *Adv Drug Delivery Rev*. 2023;198:114862. doi:10.1016/j.addr.2023.114862
119. Wendong Y, Xingxing Y, Xianze X, et al. Nanoformulation-assisted microneedle transdermal drug delivery system: an innovative platform enhancing rheumatoid arthritis treatment. *Biomed. Pharmacother*. 2024;178:117219. doi:10.1016/j.biopha.2024.117219
120. Brito S, Baek M, Bin BH. Skin Structure, Physiology, and Pathology in Topical and Transdermal Drug Delivery. *Pharmaceutics*. 2024;16(11). doi:10.3390/pharmaceutics16111403
121. Zhao L, Chen J, Bai B, et al. Topical drug delivery strategies for enhancing drug effectiveness by skin barriers, drug delivery systems and individualized dosing. *Front Pharmacol*. 2024;14:1333986. doi:10.3389/fphar.2023.1333986