

Ultrasound-Assisted Wearable Patches for Transdermal Drug Delivery

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Review Article

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Abstract

Wearable ultrasound patches represent a new class of transdermal drug delivery systems, offering a minimally invasive, programmable, and user-friendly platform for personalized therapy and precision medicine. Here, we review recent advances in ultrasound-assisted transdermal drug delivery (UATDD) with an emphasis on acoustic mechanisms and device engineering. We describe the recent evolution of UATDD from early high-energy sonophoresis to sophisticated, skin-conformal platforms that exploit advanced acoustic modalities for precise, on-demand delivery. Key innovations include bulk-wave, surface acoustic wave, and acoustic vortex-based devices, alongside the synergistic integration of ultrasound with microneedles, which transforms the patch into a localized, in situ “bioreactor.” Looking forward, UATDD systems are poised to evolve toward fully autonomous, closed-loop wearable theranostic platforms that integrate real-time biosensing with AI-driven adaptive control, but challenges remain, including long-term biocompatibility, efficient wireless power management, and clear regulatory pathways. We believe UATDD patches hold significant potential to redefine

disease management, shifting the paradigm from intermittent treatment to continuous, adaptive, and autonomous care.

Key words

transdermal delivery; drug delivery; wearable patch; ultrasound; microfluidics; acoustofluidics;

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1. Introduction

Transdermal drug delivery (TDD) has attracted significant attention as an alternative to oral and injectable administration routes, owing to their ability to bypass hepatic first-pass metabolism, non-invasiveness, and suitability for self-administration[1-3]. However, the skin, as the body's primary line of defense, presents a formidable barrier. Skin's outermost layer, the stratum corneum (SC), remains the principal impediment to TDD development[4]. The SC consists of a 15–20 μm -thick layer of keratin-filled dead cells, forming a highly ordered and dense structure that effectively prevents the ingress of exogenous substances and severely restricts the permeation of drug molecules[5]. Furthermore, inter-individual variability in skin physiology introduces significant uncertainty into the clinical application of TDD. Skin thickness, hydration, blood perfusion, and metabolic activity vary markedly across ethnicity, gender, age, and even anatomical location within the same individual[6, 7]. This variability makes the prediction and control of drug permeation rates and absorption quantities challenging, posing a formidable obstacle to achieving precise and reproducible therapeutic outcomes[8].

To overcome the SC barrier, researchers have developed various physical penetration enhancement techniques, such as iontophoresis[9], electroporation, microneedles (MNs)[10-12], and thermal ablation[13]. While these strategies can relatively enhance skin permeability, their clinical application is frequently hindered by risks including cutaneous irritation, erythema, and potential tissue damage. By comparison, Ultrasound-assisted transdermal drug delivery (UATDD) approaches offer a needle-free alternative, expanding the delivery window for macromolecular and highly hydrophilic therapeutics[14, 15]. UATDD relies on distinct modality-dependent biophysical mechanisms, including cavitation, acoustic streaming, radiation force, flow-induced shear stress, and localized thermal effects, to transiently modulate skin permeability and promote the transdermal transport of therapeutic agents[16-18].

The potential of UATDD, however, lies not only in their capacity to enhance permeation but also in their nature as an externally controllable physical trigger. Unlike chemical enhancers, whose action is passive and sustained[19, 20], the application of ultrasound can be precisely initiated and terminated, and its acoustic parameters (such as intensity, frequency, and duty cycle) can be dynamically modulated in real-time[21-27]. This exceptional controllability has driven the evolution of TDD technology from simple penetration enhancers to integrated smart patches. The core concept of a smart patch is

to co-integrate the drug reservoir, the acoustic actuation unit, and on-board diagnostics into a flexible and wearable device.

Such integration lays the foundation for on-demand, pulsatile, and quantitative drug delivery, effectively addressing dynamic dosing requirements that traditional patches cannot meet. In recent years, the integration of flexible electronics, wearable patches, and ultrasonic transducers (**Fig. 1**) has progressively made the closed-loop intelligent transdermal drug delivery a reality[17, 28, 29]. This review surveys recent advances in UATDD patches, including sonophoresis-based wearable patches (based on bulk-wave, surface acoustic wave (SAW), and acoustic vortex modalities) and ultrasound-MN hybrid patches, and also explores future directions towards the development of theranostics and intelligent closed-loop systems.

2. Wave-based ultrasound-assisted transdermal drug delivery

2.1. Bulk acoustic wave

Bulk-wave ultrasonic patches primarily utilize the cavitation effect, which is defined as the nucleation, growth, oscillation, movement, and collapse of tiny bubbles when a liquid is irradiated by ultrasound[30], to increase skin permeability[31]. Simultaneously, the thermal effects of ultrasound can also play additional roles by increasing the kinetic energy and diffusivity of drugs, dilating hair follicles and sweat glands, and enhancing local blood perfusion[3]. However, in ultrasound-assisted wearable patches, mechanical effects typically dominate in order to avoid thermal damage associated with prolonged skin contact and continuous operation.

Acoustic cavitation[32] can be induced via high frequency sonophoresis (HFS) (over 1 MHz), intermediate frequency sonophoresis (IFS) (100 kHz-1 MHz), and low frequency sonophoresis (LFS) (20-100 kHz)[5]. The small bubbles generated under HFS can nucleate cavitation within the SC, as their dimensions closely match the intercellular spacing of lipid bilayers[33]. In contrast, the larger bubbles generated by LFS are generally more effective, as they give rise to stronger transient phenomena, such as shock waves and acoustic microjets resulting from bubble collapse[18, 34]. Owing to their larger bubble size, cavitation is less likely to occur within the SC itself, but instead predominantly arises in the fluid coupling medium at the skin surface. Assuming an idealized SC matrix that is homogeneous, isotropic, and linearly elastic, with a critical failure strain of $\varepsilon_c = 0.02$, the rate of SC permeabilization induced by spherically symmetric shock waves can be expressed as[18]:

$$\frac{d\alpha}{dt} = \frac{1}{3} \eta \left(\frac{r_{\min}}{\varepsilon_c \rho c^2} \right)^3 \left(\sqrt{\frac{2\pi}{\beta^3}} \right) \quad \backslash * \text{MERGEFORMAT (1)}$$

where ρ and c correspond to the density and speed of sound of the fluid coupling medium. The parameter η describes the number of cavitation collapse events per unit volume per unit time and scales with ultrasound intensity. $r_{\min}$ denotes the minimum cavitation bubble radius, whereas β is an experimentally derived constant obtained by fitting Eq. to measured $d\alpha / dt$ values.

Alternatively, when a cavitation bubble collapses near the skin boundary, the asymmetry of the surrounding flow breaks its spherical symmetry and drives a focused microjet perpendicular to the tissue interface. Within a limited stand-off distance, and assuming an idealized jet of uniform radius (r_{jet}) and constant velocity (v_j), the rate of SC permeabilization induced by acoustic microjets can be expressed as[18]:

$$\frac{d\alpha}{dt} = \left(\frac{\pi v_j^2 r_{\text{jet}}^2}{\varepsilon_c^2 c^2} \right) \eta_{\text{jet}} \quad \backslash * \text{MERGEFORMAT (2)}$$

where η_{jet} is defined as the number of jet impacts per unit skin area per unit time. Both Eq. (1) and Eq. (2) are idealized hydrodynamic approximations of LFS and therefore omit the anisotropic three-dimensional microstructure and viscoelastic damping of real skin.

In addition, at lower ultrasound frequencies, the cavitation nucleation threshold, defined as the absolute negative pressure required for gas release or vaporization within the fluid, tends to be reduced[35]. By contrast, IFS represents a compromise between the convective effects characteristic of HFS and the strong inertial cavitation intensity associated with LFS[17].

Yu et al. developed a conformable ultrasound patch (cUSP) based on lead zirconate titanate (PZT) piezoceramics (Fig. 2b). This device embeds rigid PZT discs into a soft elastomeric PDMS substrate and forms cavitation pockets between the patch and the skin. Under excitation (~200–300 kHz), inertial cavitation can be efficiently induced within these localized pockets, leading to a significant enhancement in drug permeation flux over a short period (e.g., 10 minutes), increasing niacinamide permeation by 26.2-fold[17]. Scaling this concept to large, complex surfaces, such as the human face, introduces unique design challenges. Li et al. addressed this with a

stretchable electronic facial mask (SEFM) that integrates a PZT array into an island–bridge stretchable circuit, encapsulated within a face-shaped silicone layer (Fig. 2c). Through special fabrication techniques such as single-side soft pressing (SSSP), the SEFM maintained conformability while achieving efficient delivery of hyaluronic acid (HA), enhancing skin moisture content by 20% in human facial experiments[29].

Mechanistically, a critical boundary exists concerning the physical location of cavitation events. In low frequency systems, the resonant radius of bubbles is approximately 150 μm at 20 kHz which is far larger than the intercellular voids of the stratum corneum, thereby restricting the disruptive action to the external coupling medium via microjet impingement[5]. Conversely, high frequency ultrasound produces smaller bubbles under 1 μm that can nucleate within skin appendages or lacunar cavities, though this internal action provides significantly lower enhancement ratios compared to external collapse[5].

Several engineering and biological limitations continue to hinder the clinical translation of bulk wave systems. A significant constraint is the stochastic nature of acoustic cavitation which is highly sensitive to dissolved gas content and transducer positioning, leading to high variability in treatment outcomes[17]. Furthermore, the relationship between acoustic intensity and permeation rate is non-linear as excessive intensity causes bubbles to accumulate at the transducer surface, creating a shielding effect that reduces delivery efficiency[5, 31]. Safety boundaries are also relatively narrow because sustained exposure at intensities reaching 4 W/cm^2 has been shown to induce epidermal detachment and dermal necrosis[31]. Thermal accumulation represents another major hurdle since continuous ultrasound application can raise skin temperatures to 47°C within 10 minutes, necessitating the use of pulsed duty cycles to allow for heat dissipation[17].

2.2. Surface acoustic wave

SAW[36-55] has recently emerged as distinctive acoustic actuators to enable patch integration for TDD. Unlike the intense cavitation typically induced by conventional bulk ultrasound, SAWs offer a gentler and more skin-compatible strategy for transdermal drug delivery. SAWs are high-frequency (typically >10 MHz) mechanical waves confined to the surface of a piezoelectric substrate. When coupled to skin, their energy is concentrated within the epidermis and superficial dermis, enabling controllable penetration depth[28].

The mechanism of SAW TDD differs significantly from that of low-frequency sonophoresis. SAW-based TDD primarily relies on three synergistic effects: intense nanoscale mechanical vibration, localized acoustic streaming, and a mild acousto-thermal effect. These effects collectively act on the SC, disrupting its lipid structure and increasing the drug's diffusion coefficient, without involving intense inertial cavitation. This non-cavitation mechanism is a core advantage of SAW, enabling it to avoid the deep tissue damage and uncontrolled drug penetration associated with the intense cavitation effects of low-frequency ultrasound. This is particularly crucial in applications requiring precise drug delivery to a specific depth, such as mucosal drug delivery[56]. Ramesan et al. showed that precise control of SAW frequency, power, and exposure time can confine penetration of macromolecules (e.g., 66 kDa albumin) within mucosal layers, achieving >95% localized drug enrichment in that region while avoiding transport into the deeper, vascularized submucosa layer[56].

This controllable, localized energy not only enhances the efficacy of local treatment but also preserves the structural integrity of macromolecules, offering a safe and efficient new route for TDD. Recently, Zhang et al. reported a flexible SAW (FSAW) patch fabricated on thin aluminum foil that efficiently delivered macromolecules up to 2000 kDa, with penetration depths of ~100 μm in porcine skin tissue, highlighting potential for vaccines, antibodies, and other large therapeutics (Fig. 2e)[28].

To achieve true clinical applicability, wireless functionality is a key direction for SAW patch development. Zhang et al. have developed a SAW patch driven by wireless power transfer (WPT) technology (Fig. 2f)[57]. This device integrates a WPT coil onto the flexible patch, enabling non-contact powering via an external radiofrequency source. This eliminates the constraints of traditional cables, greatly enhancing the device's wearability, portability, and reusability. The wireless design also reduced local heating caused by wired interconnects (silver-paste bonding), thereby improving safety. In animal models, the wireless SAW system achieved ~78% of the delivery efficiency for 5 kDa hyaluronate rhodamine compared to its wired counterpart, validating the feasibility.

However, several critical limitations restrict the widespread adoption of SAW-based systems. A primary biological constraint is the inverse correlation between molecular weight and penetration depth where delivery efficiency and transport distance decrease significantly as the drug size increases[28, 56]. Additionally, the physical properties of the skin itself impose strict

applicability boundaries because higher tissue density or reduced hydration levels can lead to a tenfold reduction in delivery depth[56]. The safety window for SAW systems is also relatively narrow as input voltages exceeding 100 mV have been shown to induce nuclear condensation and cellular apoptosis in mucosal tissues[56]. Excessive power levels around 10 W can cause irreversible macroscale damage including epidermal wrinkles, moisture loss, and protein denaturation[28].

2.3. Acoustic vortex

Unlike plane waves or SAW, acoustic vortex beams carry orbital angular momentum (OAM), possess a helical phase front, and exhibit a central phase singularity with near-zero pressure. This unique physical property gives rise to two primary non-cavitation enhancement mechanisms: transversal acoustic radiation force and vortical flow-induced shear stress.

The first mechanism is a distinctive transverse acoustic radiation force (T-ARF), acting perpendicular to the propagation direction. Theoretical studies indicate that even at the piconewton (pN) level, this force can act directly on the microporous structure of the SC, physically enlarging these pores through a "twisting" or "pulling" action, thereby increasing skin permeability[35]. Based on an equivalent model describing the action on an individual SC pore (Fig. 2h), each pore within the SC is simplified as a hollow cylindrical structure with an outer diameter d_{out} and an inner diameter d_{in} . The acoustic vortex beam propagating along the z-direction can be locally approximated as an inclined plane wave characterized by an amplitude v_0 (m/s) and an incident angle θ_{in} . Assuming linear lossless wave propagation and spatially uniform isotropic acoustic impedance boundaries, the forces exerted by the T-ARF on the upper surface S_h and the inner surface S_v of the SC can be respectively expressed as[35]:

$$\langle F_h \rangle = - \int_S \left\langle \rho_0 (\mathbf{e}_x \frac{\partial \phi}{\partial x}) \frac{\partial \phi}{\partial z} \right\rangle dS \quad \text{MERGEFORMAT (3)}$$

$$\langle F_v \rangle = - \int_S \left\langle \rho_0 (\mathbf{e}_x \frac{\partial \phi}{\partial x}) \frac{\partial \phi}{\partial n_x} \right\rangle dS + \int_S \left\langle \frac{1}{2} \rho_0 \left[\left(\frac{\partial \phi}{\partial x} \right)^2 + \left(\frac{\partial \phi}{\partial y} \right)^2 + \left(\frac{\partial \phi}{\partial z} \right)^2 \right] \mathbf{n}_x \right\rangle dS - \int_S \left\langle \frac{p^2}{2c_0^2 \rho_0} \mathbf{n}_x \right\rangle dS \quad \text{MERGEFORMAT (4)}$$

where ρ_0 and c_0 correspond to the density and speed of sound of the medium. $\mathbf{e}_x$ is the fundamental vector of Cartesian coordinate system, ϕ is the velocity potential, $\mathbf{n}_x$ is the projection of the normal unit vector for each boundary $\mathbf{n}$ onto $\mathbf{e}_x$, which is $\mathbf{n}_x = (\mathbf{n} \cdot \mathbf{e}_x) \mathbf{e}_x$.

The second mechanism is localized vortical flow with high shear stress, generated by focused acoustic vortex (FAV). The helical wavefront of the FAV

induces localized, high-speed rotational fluid motion at its focus, and the resulting shear stress is calculated from the experimentally measured velocity field as[58]:

$$\tau = \varphi \left(\frac{\partial \bar{u}}{\partial y} + \frac{\partial \bar{v}}{\partial x} \right) \quad \backslash * \text{MERGEFORMAT (5)}$$

where $\bar{u}$ and $\bar{v}$ represent the time-averaged horizontal and vertical velocity components, respectively, and φ is the fluid viscosity of the medium. This vortical flow can generate shear stresses as high as 7–15 Pa, a range that approaches or falls within the biologically relevant threshold for inducing reversible cell membrane poration. Experiments have demonstrated that under same acoustic pressure, duty cycle, and sonication duration, a 1 MHz FAV can enhance the penetration depth of hydrophilic macromolecules (up to 150 kDa) in porcine skin by 2- to 3-fold compared to conventional focused ultrasound, without causing significant temperature elevation or inertial cavitation (Fig. 2i) [58]. Unlike conventional FUS, which generates outward acoustic streaming that drives drug formulations away from the target zone, FAV establishes an inward pressure gradient toward the central axis and thereby confines the fluid at the target site. Because the FAV beam is synthesized electronically through planar multichannel transducer arrays, it also avoids the geometric constraints of fixed focusing and integrates more readily into scalable system architectures[58].

It is worth noting that both mechanisms operate at acoustic intensities well below the threshold required to induce inertial cavitation, suggesting that acoustic vortex-based TDD can operate at lower, safer energy levels while still achieving high delivery efficiency, reducing risk of tissue damage. Moreover, the vortex beam's topological charge introduces a new control dimension for UATDD, enabling finer and safer drug delivery. However, several critical limitations still constrain the clinical utility of FAV-based systems. Their delivery performance is highly sensitive to acoustic operating conditions, as increasing the acoustic pressure beyond 1 MPa or the duty cycle above 60% paradoxically reduces delivery efficiency. This decline is primarily caused by a decrease in the electromechanical coupling efficiency of the piezoelectric elements as the transducer temperature rises during prolonged operation which subsequently reduces the acoustic output amplitude. Sonication duration is similarly restricted because enhancement effects have been shown to diminish when exposure exceeds 3 minutes[58]. FAV-based systems also face challenges related to beam quality and model accuracy. There is a mismatch between theoretical T-ARF distribution patterns and actual observed pore expansion, which may be attributed to the non-circular shape

of skin pores or imperfect beam formation during the phase-coded driving process[35]. Additionally, the piconewton-level forces induced by vortex beams are relatively weak and may be insufficient to overcome the mechanical integrity of high-density tissue regions if the beam phase singularity is not perfectly aligned[35]. While the modality is inherently safer due to its operation below the inertial cavitation threshold and the maintenance of tissue temperature increases below 0.5 °C, this safety window necessitates a compromise in the total magnitude of delivered energy which may limit its application for drugs requiring deep systemic circulation access beyond the superficial dermal layers[58]. Overall, the cavitation-dominant mechanism of conventional BAW delivers a higher transient flux, but the acoustic intensities it requires can cause epidermal detachment or dermal necrosis, and the stochastic collapse of inertial cavitation makes drug retention and depth localization difficult to control. Non-cavitation methods such as SAW and acoustic vortices instead open transport channels through high-frequency micro-vibration, steady acoustic streaming, or transverse radiation force, achieving spatially controllable, lower-intensity channel opening that improves delivery precision and widens the safety window.

3. Microneedle-based ultrasound-assisted transdermal drug delivery

MN technology, particularly dissolving MNs (DMNs)[59, 60], offers a minimally invasive and painless solution for UATDD. DMNs are micro-scale needle arrays fabricated from biocompatible and degradable materials, such as hyaluronic acid and gelatin, which are pre-loaded with drugs or nanoparticles. When the patch is pressed onto the skin, the needle tips penetrate the SC to reach the epidermis or superficial dermis, gradually dissolving in the tissue fluid, releasing their payload in situ. In addition to DMNs, other types of MN are also utilized, such as solid MNs for skin pre-treatment and acoustic metamaterial that integrate drug delivery, both of which effectively create micron-scale channels through the skin.

3.1. Enhanced dissolution and diffusion

For DMNs, the application of ultrasound produces a significant synergistic enhancement. First, the mechanical vibrations and micro-perturbations generated by the ultrasound waves can markedly accelerate the dissolution of the DMN, leading to a faster release of the drug. Second, the acoustic radiation force and pressure gradients from the ultrasound actively drive the drug molecules or nanoparticles released from the DMN into the surrounding tissue, overcoming the limitations of passive diffusion. Experiments have shown that ultrasound can double the penetration depth compared to the non-ultrasound control group (Fig. 3b)[61].

3.2. On-demand activation of ultrasound-responsive nanoparticles

The synergy between ultrasound and MNs enables on-demand activation, where DMNs are responsible for delivering functional, ultrasound-responsive nanoparticles, and ultrasound serves as a secondary external trigger to activate these nanoparticles in situ to perform therapeutic functions.

3.2.1. Piezocatalytic Nanoparticles

A frontier strategy utilizes DMNs to deliver piezoelectric nanoparticles, such as modified mKNNs (Fig. 3c)[62] or zinc porphyrin-based metal-organic framework and zinc oxide (ZnTCPP@ZnO) (Fig. 3d)[63]. When subjected to ultrasonic mechanical stress, these nanomaterials undergo charge separation and generate transient electric fields. The electric fields catalyze the generation of reactive oxygen species (ROS) from surrounding water and oxygen, which can effectively kill pathogens or tumor cells. In cancer immunotherapy, mKNNs nanoparticles delivered by DMNs and activated in situ by an integrated flexible ultrasound patch generate ROS that induce immunogenic cell death (ICD) in tumor cells and modulate macrophage polarization. When combined with a PD-1 antibody, this approach may effectively inhibit distant tumor growth and recurrence[62]. In the treatment of bacterial skin infections, the ROS generated by ZnTCPP@ZnO nanoparticles under ultrasound achieve a 99.73% kill rate against *Propionibacterium acnes*. Meanwhile, the zinc ions released from the nanoparticles promote fibroblast proliferation, accelerating skin repair[63].

3.2.2. Sono-chemical and sonothermal synergistic nanoparticles.

Another synergistic therapeutic strategy utilizes ultrasound to trigger multiple treatment modalities simultaneously. For instance, CuO₂/TiO₂ heterostructure nanoparticles loaded into HA MNs have been used for treating drug-resistant wound infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. 3e)[64]. In this system, ultrasound not only activates TiO₂ to produce ROS (sonodynamic therapy) but also triggers a Fenton-like reaction in CuO₂ to convert hydrogen peroxide into more toxic hydroxyl radicals (chemodynamic therapy). Simultaneously, the material's excellent sonothermal conversion efficiency generates localized hyperthermia (sonothermal therapy). This multi-modal synergistic action can achieve a kill rate of up to 99.9999% against resistant bacteria within 5 minutes and significantly accelerates wound healing. This delivery-activation strategy turns the drug delivery patch into an in situ bioreactor. Therapeutic agents, such as ROS, are produced on-demand at the required time and location. The resulting spatiotemporal precision broadens the therapeutic window for agents

with potential systemic toxicity and holds promise for localized treatment of tumors and infections, enabling truly on-demand pharmacodynamics. To translate this in situ bioreactor toward clinical use, the platforms can be fabricated by vacuum casting biocompatible HA in molds, a method that offers high manufacturing scalability, reproducible drug loading, and low production cost.

3.3. Active delivery by acoustic streaming

Xu et al. have leveraged MN metamaterial patch to achieve active drug delivery (Fig. 3f,g) [65, 66]. The sharp metamaterial structures of the patch can create micron-scale pathways in the skin to increase permeability. By generating localized acoustic streaming, the device can actively drive drugs from the porous metamaterial structures into the superficial dermis and deep tissues. This design effectively turns each MN into a micropump that actively infuses the drug into the dermis. In a mouse model of anaphylactic shock, this device successfully reversed the critical state through a multi-burst delivery of epinephrine, demonstrating superior efficacy compared to the conventional fixed-dosage EpiPen injection, particularly in severe anaphylactic reactions[65]. This active delivery method not only significantly increases the delivery rate and dosage but also enables precise control over pharmacokinetics, which is valuable for acute conditions that require rapid, on-demand dosing.

3.4. Current Limitations and Translational Barriers

Although the combination of ultrasound and MN arrays offers a compelling strategy for rapid and site-specific drug delivery, several unresolved challenges continue to hinder clinical translation. A central limitation is payload compatibility, as the aqueous microchannels formed after MN insertion preferentially support the transport of hydrophilic compounds, while hydrophobic agents remain difficult to deliver efficiently[67, 68]. Clinical implementation is further restricted by biosafety concerns, since even minimally invasive MN penetration may still cause local adverse effects such as erythema, edema, and infection[57]. These biological and engineering constraints are compounded by high manufacturing costs and limited treatment coverage, which together remain significant barriers to large-scale clinical adoption.

4. Wearable ultrasound and sensing patches

The transition from rigid clinical equipment to wearable patches requires a fundamental shift in material science and structural engineering. Conventional ultrasound equipment relies on rigid and cumbersome piezoelectric ceramic

probes, which restricts their application in mobile healthcare[15]. To achieve sustained and comfortable applications, researchers have developed flexible acoustic patches that conform to dynamic body surfaces[69-71].

4.1. Design principles of wearable ultrasound patches

The selection of materials for wearable ultrasound patches has transitioned from an emphasis on isolated functional attributes toward a holistic integration of electromechanical conversion efficiency, mechanical flexibility, and long term biosafety[72]. While early designs relied extensively on high performance piezoelectric ceramics or intrinsically flexible polymers such as polyvinylidene fluoride (PVDF) [73-76], the field is increasingly prioritizing lead-free alternatives like sodium potassium niobate and barium titanate to circumvent the toxicity risks associated with conventional lead-based components[77, 78]. Current materials engineering strategies emphasize the development of sophisticated multimaterial composites that combine the high piezoelectric output of inorganic fillers with the biocompatibility of natural polymers or hydrogels[79, 80]. These integrated systems aim to overcome the persistent trade-off between device sensitivity and the structural resilience required for conformable skin attachment though they introduce complexities regarding manufacturing scalability and interfacial stability. In terms of structural engineering, flexible ultrasound patches often adopt an island bridge configuration. Small, rigid piezoelectric elements are embedded into a soft substrate and connected by stretchable serpentine electrodes[81]. This geometric topology allows the device to maintain stable acoustic performance and electrical connectivity under tensile strains exceeding 170%[82]. Encapsulation within biocompatible elastomers further enables these arrays to conform to and adhere long term to complex anatomical shapes such as the carotid artery or the precordial region[83].

4.2. Sensing modules

Beyond drug delivery, Ultrasound-Assisted Wearable Patches are emerging as multifunctional medical tools with powerful imaging and diagnostic capabilities[14]. These devices provide continuous, non-invasive, and real-time monitoring of deep tissues, forming the essential "sensing" component of a closed-loop theranostic system. The diagnostic applications of wearable ultrasound patches are extensive[84]. In cardiovascular assessment, patches integrating B-mode and M-mode imaging can capture dynamic cardiac structures, such as myocardial wall motion, to evaluate heart function during rest and exercise (Fig. 4a)[70, 71, 85]. Furthermore, wearable ultrasound patches can non-invasively monitor haemodynamic parameters. A-mode signals can measure arterial wall pulsations to monitor blood pressure at

multiple locations (Fig. 4b,c)[86-90], while transcranial Doppler can measure blood flow to identify issues like arterial stenosis or monitor cerebral blood flow for early stroke detection (Fig. 4d)[69, 91-93]. In musculoskeletal evaluation, these patches can be used to evaluate muscle contraction and training intensity[94, 95], track post-exercise recovery (Fig. 4e)[96], and assess bone fracture healing[97]. The wearable ultrasound patches also enable continuous monitoring of internal organs, including the breast for early tumor detection (Fig. 4f) [98, 99], the bladder for volume measurement (Fig. 4g)[100-103], the stomach for digestive health monitoring (Fig. 4h)[69, 104], the liver for fibrosis and cirrhosis evaluation[105], and the lungs for monitoring lung functionality[70, 106-110]. Integration with complementary sensors enables wearable ultrasound patches to perform multimodal monitoring, further enhancing diagnostic accuracy and advancing personalized healthcare[111-113]. For instance, integrating with electrochemical sensors enables simultaneous monitoring of blood pressure and lactate levels during exercise (Fig. 4i)[88]. In another approach, wearable photoacoustic probes, integrating with compact optical components, are able to generate high-contrast biomolecular images, offering potentials for monitoring blood perfusion (Fig. 4j,k) [114, 115]. The real-time data gathered from these imaging and diagnostic modules provides the direct physiological input required for the AI-driven control algorithms that enable a truly adaptive, closed-loop therapeutic system[116, 117].

5. Challenges and outlooks

UATDD has evolved from cavitation-dominant bulk-wave patches toward more refined, non-cavitation modalities, including SAW, acoustic vortex, and synergistic strategy with MNs. This development reflects a shift from energetic disruption to precise physical manipulation, enabling safer and more controlled delivery of a wide range of therapeutics. Continuous sensing can directly govern therapeutic intervention, forming an autonomous closed-loop theranostic system. For example, multimodal time-series analysis of electrochemical and ultrasound signals could detect rapid hyperglycemic excursions and trigger ultrasound-mediated insulin delivery to restore glycemic control. In chronic inflammation and solid tumors, real-time photoacoustic measurement of vascular dilation or tumor hemodynamics could guide adaptive adjustment of acoustic intensity and exposure time. By coupling delivery to physiologically defined thresholds, the patch can regulate transdermal release of anti-inflammatory agents or chemotherapeutics at the required time and dose, improving local efficacy while limiting systemic exposure and off-target toxicity.

Wearable ultrasound patches represent significant progress toward the ultimate goal in advanced drug delivery: the creation of autonomous, intelligent systems. As conceptually illustrated in Fig. 5, this paradigm is centered on a closed-loop system where a wearable ultrasound patch performs real-time sensing and drug delivery system. Although commercial systems such as the U-Strip™ patch (Transdermal Specialties, Inc.) have achieved needle-free insulin delivery[118], a fully integrated closed-loop theranostic platform that couples automated drug release with ultrasonic biosensing patches remains a challenge. The sensing data is processed by an AI control unit, which commands a driver module to trigger a precise, on-demand therapeutic dose. This sense-decide-delivery cycle enables the system to adapt dynamically to the patient's needs, paving the way for personalized medicine. The developmental trajectory of UATDD is clearly leading towards a highly integrated platform, involving sensing, control, and actuation functions to create a wearable theranostic platforms on the skin with support of microfluidics and electronics[119-127]. However, realizing this vision requires solving several open problems, including maintaining robust skin adhesion during repeated use, ensuring safe device sterilization, and optimizing wireless power management. Patient compliance and regulatory pathways also diverge sharply among cosmetic, acute-care, and chronic-disease applications, each demanding distinct standards for hardware reliability and data privacy. Despite these challenges, the transformative potential of intelligent UATDD systems is immense. It could shift chronic-disease management from episodic, reactive interventions to continuous, proactive, and autonomous care. The ultimate goal is not merely a better delivery tool but a surrogate physiological function that offloads dysregulated processes to an external intelligent system, with the potential to fundamentally change how patients live with chronic conditions and to reduce the burden of day-to-day self-management.

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Author contributions

J.L. wrote the original draft. F.C., Y.Y., K. M., and F.G. edited the manuscript.

Competing financial interests

The authors declare that they have no competing financial interests.

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Figure and captions

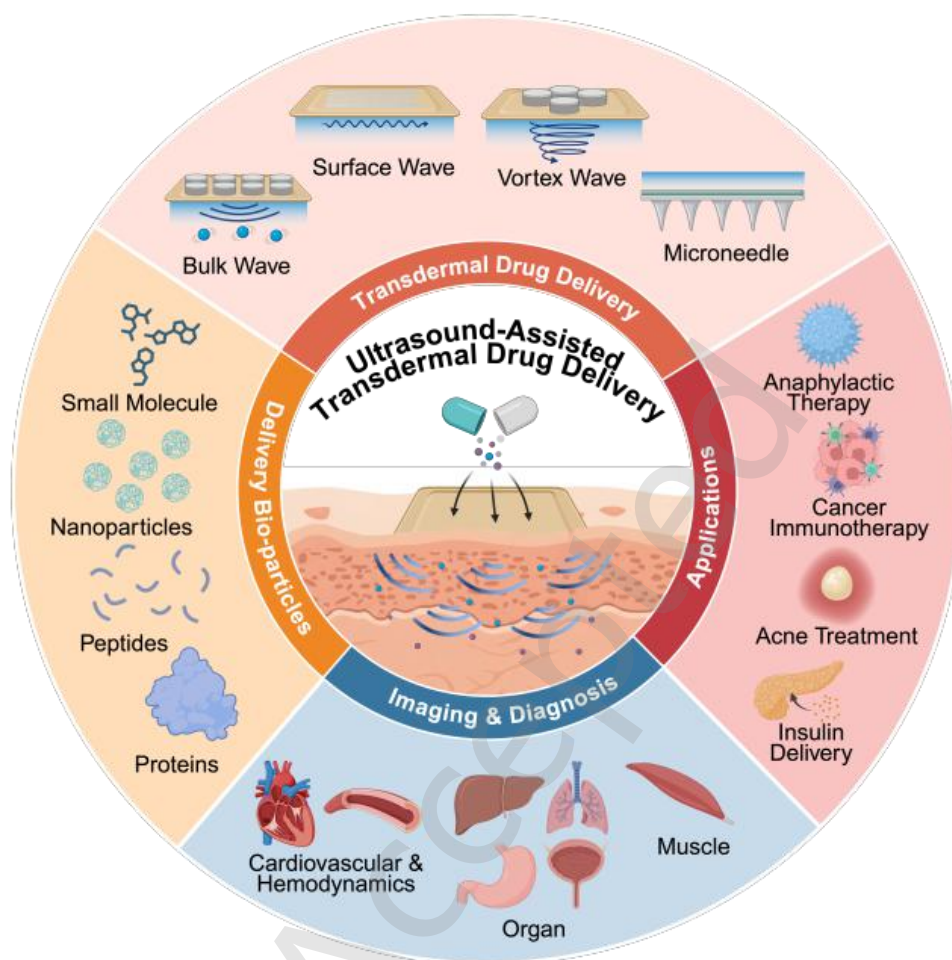


Fig. 1 Overview of the wearable ultrasound-assisted transdermal drug delivery (UATDD) patches.

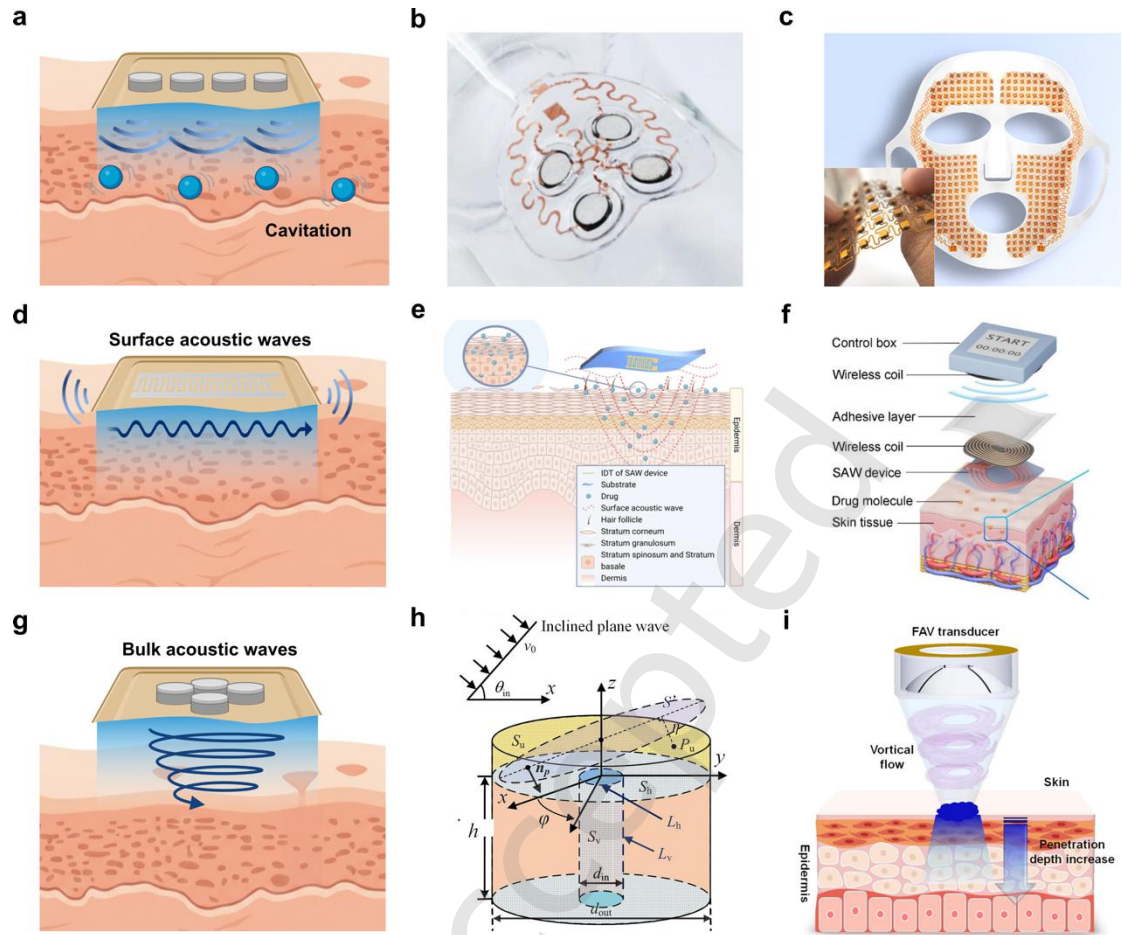


Fig. 2 Sonophoresis-based wearable TDD patches. (a) Schematic illustration of bulk acoustic wave UATDD. (b) Photograph of the 2D-array of conformable ultrasound patch (cUSP)[17]. (c) Inside view of the SEFM and optical image of the stretchable island-bridge mesh circuit[29]. (d) Schematic illustration of surface acoustic wave UATDD. (e) Drug delivery mechanisms and route induced in the skin layers using the SAW technique[28]. (f) Schematic of the wirelessly powered SAW TDD system[57]. (g) Schematic illustration of acoustic vortex UATDD. (h) Sketch map of the hollow cylinder model[35]. (i) Illustrative schematic of the mechanistic role of FAV-induced vortical streaming[58].

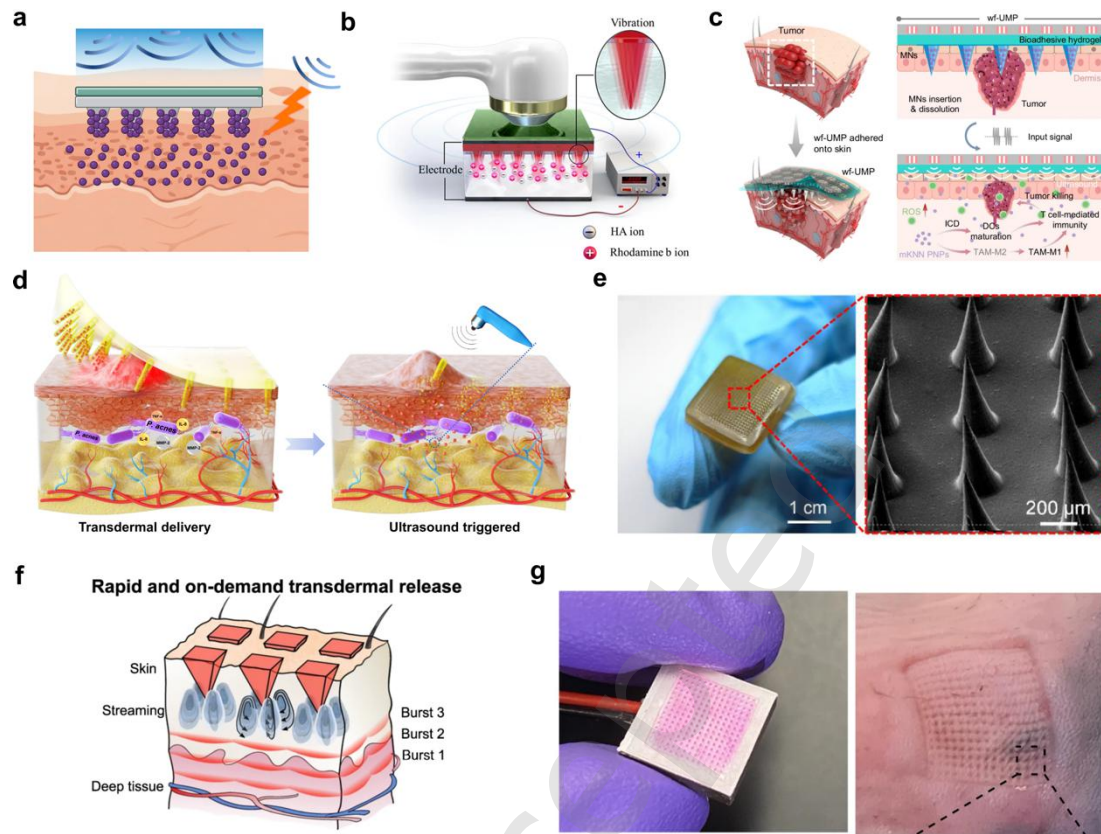


Fig. 3 UATDD with microneedles (MNs). (a) Schematic illustration of UATDD with DMNs. (b) multi-system structure of HA MNs UATDD[61]. (c) Schematic illustration of the operational procedure of wf-UMP for tumor immunotherapy[62]. (d) MN UATDD patch for acne treatment[63]. (e) MN UATDD patch for antibacterial wound treatment[64]. (f, g) Active drug delivery using a metamaterial UATDD patch[65].

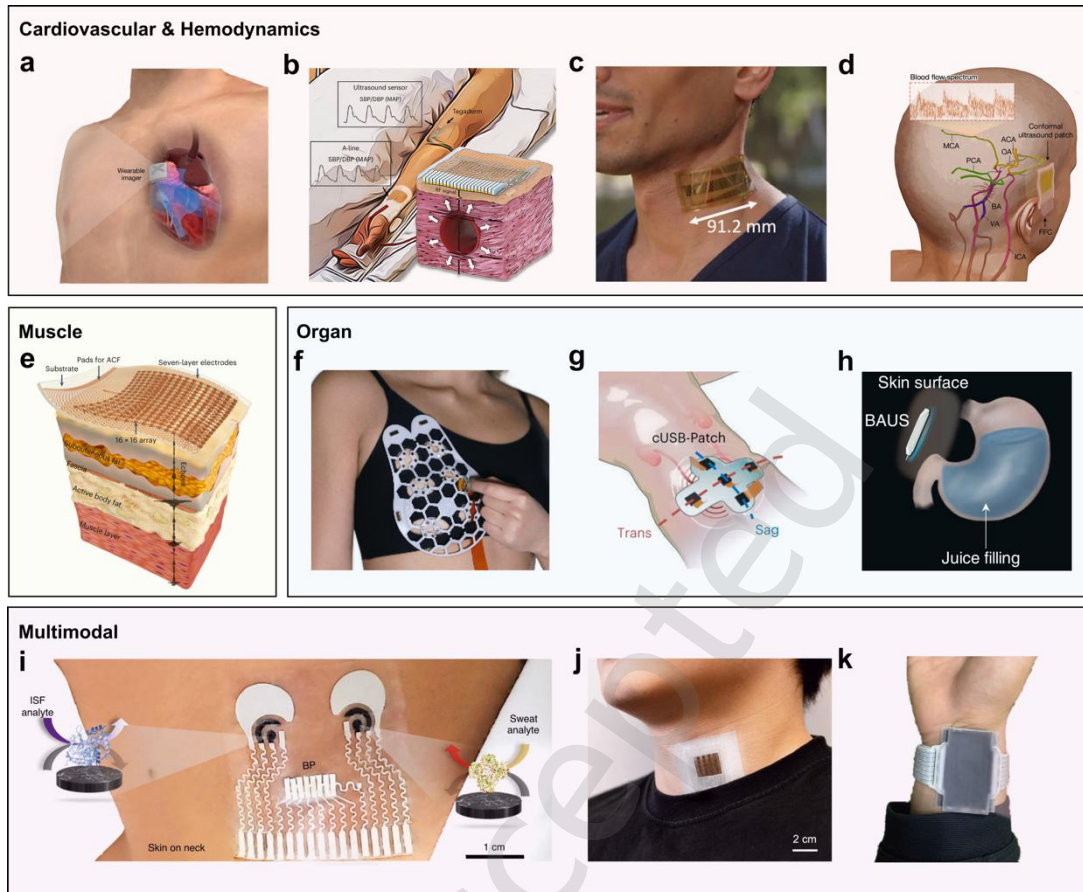


Fig. 4 Imaging and diagnostic applications of wearable ultrasound patches. (a-d) Cardiovascular assessment, including monitoring of the left ventricle[71], an artery on the arm[86], the carotid artery[87], and major arteries in the brain[69]. (e) Muscle evaluation of soft tissue[96]. (f) Breast examination for early tumor detection[98]. (g) Bladder monitoring for volume measurement[101]. (h) Stomach monitoring for digestive health[70]. (i-k) Multimodal monitoring. (i) Integration with electrochemical sensors for simultaneous monitoring of blood pressure and lactate levels during exercise[88]. (j,k) Integration with compact optical components for high-contrast visualization of biomolecules[114, 115].

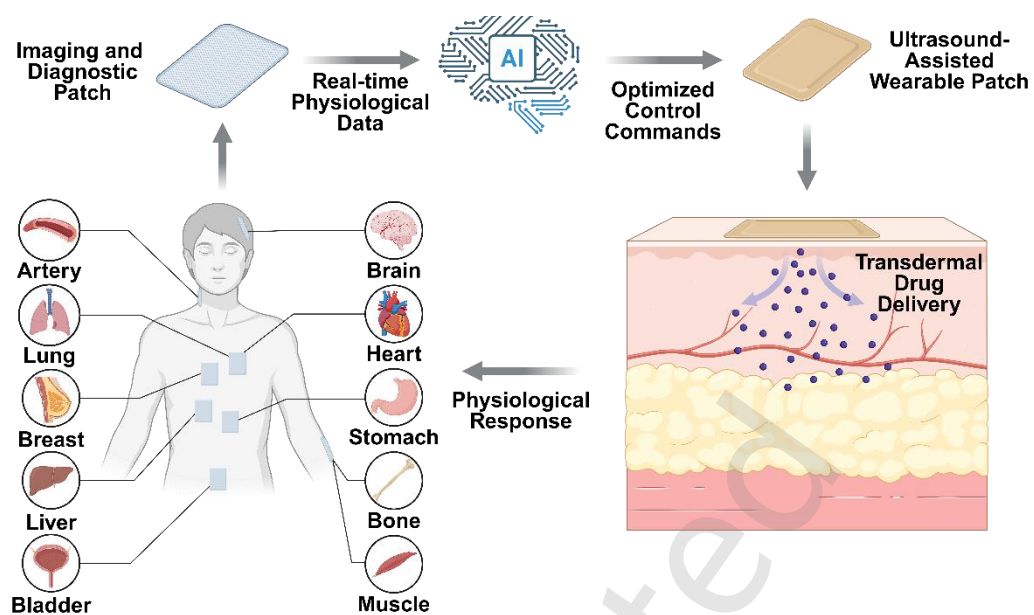


Fig. 5 Conceptual illustration of an AI-driven closed-loop UATDD system.

Table. 1 Overview of ultrasound-assisted transdermal drug delivery technologies

<i>Technology</i>	<i>Operating Frequency</i>	<i>Acoustic Intensity</i>	<i>Penetration Depth</i>	<i>Dominant Mechanism</i>	<i>Applicable drug types</i>	<i>Delivery efficiency</i>	<i>Safety Window</i>	<i>Translational Potential</i>	<i>Primary Limitations</i>
Bulk Acoustic Wave (BAW)	20 kHz– ~1MHz	~1 – 2 W/cm ²	~100 µm	Inertial cavitation, shock waves, microjets, thermal effects	Small-molecule cosmeceuticals (e.g., Niacinamide ~122 Da, D-panthenol ~205 Da), macromolecules (e.g., Hyaluronic acid 5 kDa, Beta-glucan 100 kDa)	Up to 26.2-fold enhancement vs. passive diffusion; permeation rate 13.2x faster than MNs; +20% skin moisture	Maintains epidermal/dermal integrity; cell viability >98%; local temperature safely controlled at 42–47 °C via duty cycles	Enables hands-free, conformal wearable patches for large-area delivery	High stochastic variability, thermal accumulation, narrow safety window
Surface Acoustic Wave (SAW)	10–55 MHz	-	25–100 µm in porcine skin, 400–1000 µm in mucosal tissue, up to ~1900µm	Non-cavitation, nanoscale vibration, acoustic streaming, mild acousto-thermal effects	Small molecules (e.g., Fluorescein), ultra-large hydrophilic macromolecules (e.g., Albumin, FITC-dextran up to 2000 kDa).	Up to 17.69% transmission rate across porcine skin (vs. 1.53% passive). Exhibits >95% mucosal retention for small molecules and ~60% for large proteins.	Maintains protein α-helical structures and high cell viability, with local temperatures < 35 °C	Flexible patches and battery-free, wirelessly powered systems	Highly sensitive to skin hydration and density

Technology	Operating Frequency	Acoustic Intensity	Penetration Depth	Dominant Mechanism	Applicable drug types	Delivery efficiency	Safety Window	Translational Potential	Primary Limitations
Acoustic Vortex Wave	1 MHz [35, 58]	~2 – 3 W/cm ²	Up to ~400 µm	Non-cavitation, T-ARF and vortical shear stress	Small hydrophilic molecules (e.g., Glycerin ~92 Da; Evans Blue 960 Da), macromolecules (e.g., FITC-dextran up to 150 kDa)	3.3-fold deeper penetration ex vivo and a 1.8-fold increase in vivo compared to FUS	No inertial cavitation. Negligible thermal elevation (< 0.5 °C). High cellular viability (> 98%)	Microbubble-free, non-invasive delivery platform without tissue damage	Sensitive to acoustic parameters, weak piconewton forces, beam alignment
MNs + Ultrasound	~1 MHz	~1.0 – 1.5 W/cm ²	Depends on MNs	Enhanced dissolution and diffusion, on-demand activation, acoustic streaming	Small molecules, macromolecules (e.g., epinephrine), functional nanoparticles	2- to 9.3-fold release amount increase vs. passive diffusion	Local temperature $s < 45^{\circ}\text{C}$	Wearable, flexible acoustic patches for on-demand self-administration and localized tumor immunotherapy.	Poor compatibility with hydrophobic agents, local biosafety risks, complex manufacturing, payload capacity constraints of MN arrays.