

Recent Advances in Ultrasound-Guided Drug Delivery and Therapeutic Ultrasound: Mechanisms, Nanocarriers, and Clinical Translation

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Received: 23-07-2025

Accepted: 19-09-2025

Published: 02-10-2025

ABSTRACT

Ultrasound-guided drug delivery (UGDD) and therapeutic ultrasound (TUS) have emerged as innovative approaches for improving the efficacy, specificity, and safety of pharmacological interventions. By leveraging acoustic energy, these modalities enable spatially and temporally controlled drug release, facilitate targeted delivery, and reduce systemic toxicity. This review consolidates recent advances, focusing on mechanisms such as cavitation, sonoporation, acoustic radiation force, and thermal effects; novel ultrasound-responsive nanocarriers including liposomes, micelles, nanobubbles, and phase-change droplets; and the current status of clinical translation. Preclinical and early clinical studies highlight promising therapeutic outcomes and the potential for personalized treatment. Despite these advances, challenges remain in standardizing ultrasound parameters, optimizing nanocarrier design, ensuring safety, and navigating regulatory pathways. Addressing these challenges is essential for bridging the gap between bench research and clinical application.

KEYWORDS: Ultrasound-guided drug delivery; therapeutic ultrasound; nanocarriers; microbubbles; sonoporation; clinical translation.

INTRODUCTION

Traditional drug delivery methods often face significant limitations, including poor specificity, limited bioavailability at target sites, and systemic side effects. Chemotherapeutic agents, for example, frequently affect healthy tissues, leading to dose-limiting toxicities and suboptimal therapeutic outcomes. These challenges have catalyzed the search for controlled, site-specific drug delivery systems that minimize off-target effects while maximizing therapeutic efficacy. Ultrasound-guided drug delivery (UGDD) and therapeutic ultrasound (TUS) have emerged as promising strategies to address these limitations.

Ultrasound is a versatile physical modality that has long been used for diagnostic imaging. Over the past two decades, its therapeutic potential has been increasingly recognized. In UGDD, ultrasound serves multiple roles: it can enhance vascular and cellular permeability, trigger drug release from carriers, and im-

rove localized drug accumulation (1,2). These effects are mediated through both mechanical and thermal phenomena. Mechanical effects include stable and inertial cavitation, sonoporation, and acoustic radiation forces, while thermal effects involve localized heating, which can enhance drug release from thermosensitive carriers (3).

Recent research has focused on integrating UGDD with advanced nanocarrier systems to maximize the therapeutic index. Liposomes, polymeric micelles, nanobubbles, and phase-change droplets can encapsulate chemotherapeutic, genetic, or immunotherapeutic agents, protecting them during circulation and releasing them in response to ultrasound stimulation (4). Ultrasound also enables real-time imaging-guided therapy, allowing clinicians to monitor drug delivery and tissue response noninvasively. This dual functionality—therapeutic and imaging capability—offers significant potential for personalized medicine.

Furthermore, UGDD and TUS are being investigated beyond oncology. Applications include neurological disorders (enhancing blood-brain barrier permeability), cardiovascular diseases (targeted thrombolysis), and tissue engineering (ultrasound-triggered scaffolds and drug-eluting implants) (4). However, clinical translation is challenged by the complex interplay of ultrasound parameters, nanocarrier properties, tissue heterogeneity, and safety considerations. The optimization of these factors is crucial to achieve consistent, reproducible therapeutic outcomes.

This review aims to provide a comprehensive synthesis of recent advances in UGDD and TUS, highlighting mechanistic insights, nanocarrier innovations, and translational progress. By consolidating current knowledge, we seek to identify research gaps and chart pathways toward effective clinical application.

AIM

This review aims to summarize the underlying mechanisms by which ultrasound enhances drug delivery, examine the design and function of recent ultrasound-responsive nanocarriers, and evaluate the current status, opportunities, and challenges in clinical translation.

MATERIALS AND METHOD

A systematic literature search was conducted using PubMed, Web of Science, and Google Scholar for peer-reviewed articles published up to August 2025. Search terms included “ultrasound drug delivery,” “ultrasound-responsive nanocarriers,” “therapeutic ultrasound,” “microbubbles sonoporation,” and “clinical translation ultrasound drug delivery.” Both review and original research articles were included, with preference given to studies published in the last five years. Key articles (1–4,9–11) were used to synthesize mechanistic insights and translational progress.

Recent Advances

Mechanisms of Ultrasound-Guided Drug Delivery

- 1. Cavitation and Sonoporation** Ultrasound induces oscillations in microbubbles (cavitation) that can transiently permeabilize cell membranes, a phenomenon known as sonoporation (5). Stable cavitation generates microstreaming that enhances drug diffusion, while inertial cavitation produces localized shockwaves capable of creating pores in cellular and endothelial membranes.
- 2. Acoustic Radiation Force and Microstreaming** Acoustic radiation forces push nanocarriers toward vessel walls, increasing local drug concentration. Microstreaming enhances convective transport, facilitating drug penetration into tissues (6).
- 3. Thermal Effects** Focused ultrasound can generate localized hyperthermia, which triggers release from thermosensitive carriers and may enhance cellular uptake by increasing membrane fluidity (7).
- 4. Jetting Mechanisms** Cyclic microjets formed by ultrasound-stimulated microbubbles have been visualized to puncture cell membranes, significantly increasing molecular uptake at lower acoustic pressures than previously considered (8).

Nanocarriers for Ultrasound-Responsive Delivery

- 1. Microbubbles and Nanobubbles** Nanobubbles penetrate tumors more effectively than microbubbles and can release drugs upon ultrasound stimulation. They are being developed for targeted cancer therapy and imaging-guided drug release (9).
- 2. Liposomal Systems** Ultrasound-triggered liposomes allow spatially controlled drug release, improving tumor targeting and reducing systemic toxicity (10).

3. Phase-Change Droplets Acoustic droplet vaporization converts perfluorocarbon droplets into microbubbles, triggering controlled release. Dual-trigger systems combining pH and ultrasound responsiveness enhance tumor specificity (11).

4. Polymeric Micelles Ultrasound-sensitive polymeric micelles collapse under acoustic energy to release drugs, enabling temporal and spatial control (4).

Clinical Translation

UGDD and TUS are being explored in oncology, neurological disorders, cardiovascular therapy, and tissue engineering. Real-time imaging integration enables monitoring of drug distribution and treatment response (5,9). Ultrasound-printed implants have been investigated in animal models, demonstrating precise localized delivery and implant formation guided by imaging (11). Challenges for clinical translation include optimizing ultrasound parameters, ensuring carrier stability and biocompatibility, and navigating regulatory hurdles (5,7).

DISCUSSION

The recent decade has seen remarkable progress in UGDD and TUS, characterized by the convergence of physics, nanotechnology, and clinical medicine. Understanding mechanistic underpinnings—cavitation, sonoporation, microstreaming, and thermal effects—has enabled more precise engineering of therapeutic strategies. The discovery of cyclic microjetting, for example, reveals that efficient drug delivery can occur at lower ultrasound pressures than previously believed, reducing risks of tissue damage (8).

Nanocarrier innovation has paralleled mechanistic discoveries. Liposomes remain foundational in ultrasound-triggered therapy due to their biocompatibility and ease of functionalization. Nanobubbles provide enhanced penetration and imaging contrast, while phase-change droplets and smart prodrug systems offer sophisticated dual-trigger control. This layered approach—combining mechanical, thermal, and chemical triggers—represents a shift toward highly customizable, patient-specific therapy (12).

Preclinical studies demonstrate significant improvements in tumor suppression, targeted gene delivery, and tissue regeneration. For instance, ultrasound-activated prodrug-loaded liposomes showed potent anticancer effects while minimizing systemic toxicity in murine models (13). Similarly, dual-trigger nanodroplets achieved up to 89% cumulative drug release under controlled conditions (14). Integration with imaging modalities allows real-time monitoring, providing crucial feedback for treatment optimization.

Despite these advances, translational challenges persist. Ultrasound parameter optimization is critical, as efficacy depends on acoustic frequency, pressure, duty cycle, and exposure duration. Tissue heterogeneity complicates standardization, especially in tumors with irregular vasculature. Carrier stability, immunogenicity, and long-term safety remain key concerns. Additionally, regulatory pathways for ultrasound-responsive nanomedicines are not fully defined, particularly for dual-trigger systems or in situ-formed implants (15).

Emerging strategies, such as ultrasound-assisted 3D printing of drug-loaded scaffolds, demonstrate the potential to bypass systemic circulation entirely, offering minimally invasive, localized therapy (16). However, these approaches raise new questions regarding biodegradability, long-term safety, and regulatory classification.

Overall, the integration of mechanistic understanding, nanocarrier engineering, and imaging-guided therapy is creating a robust platform for next-generation drug delivery.

Addressing translational challenges will require multidisciplinary collaboration among engineers, clinicians, regulatory experts, and pharmacologists.

CONCLUSION

Ultrasound-guided drug delivery and therapeutic ultrasound are rapidly advancing technologies with the potential to transform precision medicine. Mechanistic insights, innovative nanocarriers, and imaging-guided strategies are converging to enhance therapeutic efficacy while minimizing side effects. However, clinical translation requires standardized ultrasound protocols, rigorous safety assessment, scalable carrier production, and regulatory clarity. Multidisciplinary efforts are critical to bridge preclinical successes to clinical practice, paving the way for personalized, minimally invasive treatments.

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How to Cite: Helmi N M, Albokhari A K, Meriky L H, Alshaikh A F, Alraqdi A A, Mahmoud K K et al. Recent Advances in Ultrasound-Guided Drug Delivery and Therapeutic Ultrasound: Mechanisms, Nanocarriers, and Clinical Translation. *Radiol Med.* 2025 October 19(3):23-25.