Acoustically activatable liposomes: An innovative platform for targeted drug delivery and neuromodulation

Lili Liu,[1] Meiqi Chang,[2,*] and Yu Chen[1,3,4,*]

[1]School of Medicine, Shanghai University, Shanghai 200444, China

[2]Science and Technology Innovation Center, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200071, China

[3]Materdicine Lab, School of Life Sciences, Shanghai University, Shanghai 200444, China

[4]Shanghai Institute of Materdicine, Shanghai 200051, China

*Correspondence: changmeiqi@vip.sina.com (M.C.); chenyuedu@shu.edu.cn (Y.C.)

Received: October 29, 2025; Accepted: March 23, 2026; Published Online: March 23, 2026; https://doi.org/10.59717/j.xinn-mater.2026.100212

Citation: Liu L., Chang M. and Chen Y. (2026). Acoustically activatable liposomes: An innovative platform for targeted drug delivery and neuromodulation. *The Innovation Materials* **4**:100212.

In the field of biomedical engineering, achieving precise spatiotemporal control over drug delivery is a core objective. In particular, focused ultrasound (FUS) has emerged as a highly promising externally triggered modality due to its non-invasive nature, adjustable tissue penetration depth, exceptional focusing capability, and established clinical foundation. Nevertheless, research over the past two decades has demonstrated that the clinical translation of ultrasound-responsive nanotechnologies entails greater complexity than originally envisioned.[1] A fundamental challenge involves reconciling the inherent trade-offs among high triggering efficiency, favorable biosafety profiles, and translational feasibility. Current mainstream technical platforms all exhibit significant limitations: While perfluorocarbon-based nanoemulsions and microbubbles enable efficient drug release through inertial cavitation, they carry risks of tissue damage, low drug loading efficiency, and poor stability. Thermosensitive liposomes require local heating to phase transition temperatures, posing challenges of uneven heat distribution and thermal injury risks in practical applications. Furthermore, most nanocarriers face challenges in clinical translation due to insufficiently validated material safety and complex preparation processes, which hinder large-scale production.[2]

A Stanford University research team has proposed a groundbreaking ultrasound-triggered drug delivery strategy, marking a conceptual shift from reliance on "chemical complexity" to the pursuit of "physical innovation". They abandoned traditional high-risk mechanisms or complex new materials, instead focusing on fundamental physical principles. The core approach involves modulating the acoustic properties of the aqueous core within liposomes, such as enhancing acoustic impedance by adding safe sucrose to create a pronounced acoustic mismatch with the surrounding medium. This design enables low-energy ultrasound to effectively act upon the liposome membrane, synergizing with the pre-established transmembrane osmotic gradient to jointly drive rapid drug release. This synergistic mechanism combining acoustic mismatch and osmotic pressure force successfully achieves efficient, controllable drug release without introducing exogenous components. It offers a safer, more clinically translatable solution to overcome the longstanding trade-off between efficacy and safety in this field.[3]

The acoustically activatable liposomes (AALs) platform, constructed based on this principle, offers advantages that extend beyond conventional validation *in vitro*. The research team achieved a leap from "proof-of-concept" to "functional realization". They confirmed that the platform possesses rare broad-spectrum drug compatibility, successfully loading and enabling controlled release of drugs with diverse properties, ranging from water-soluble small molecules (e.g., ketamine) to hydrophobic local anesthetics (e.g., ropivacaine). More importantly, the team accomplished precise spatiotemporally controlled neuromodulation in rat models. Through FUS exposure, they not only delivered ketamine selectively to discrete brain regions, including the medial prefrontal cortex (mPFC) and retrosplenial cortex (RsC), eliciting region-specific electrophysiological signatures and behavioral responses, but also attained reversible sciatic nerve blockade with ropivacaine in the peripheral nervous system (Figure 1). The success of this technical strategy establishes a new benchmark for the field, highlighting that superior clinical translation potential stems not from structural complexity, but from the ingenious application of fundamental physical principles coupled with a profound understanding of clinical constraints.[4] From a research perspective, this

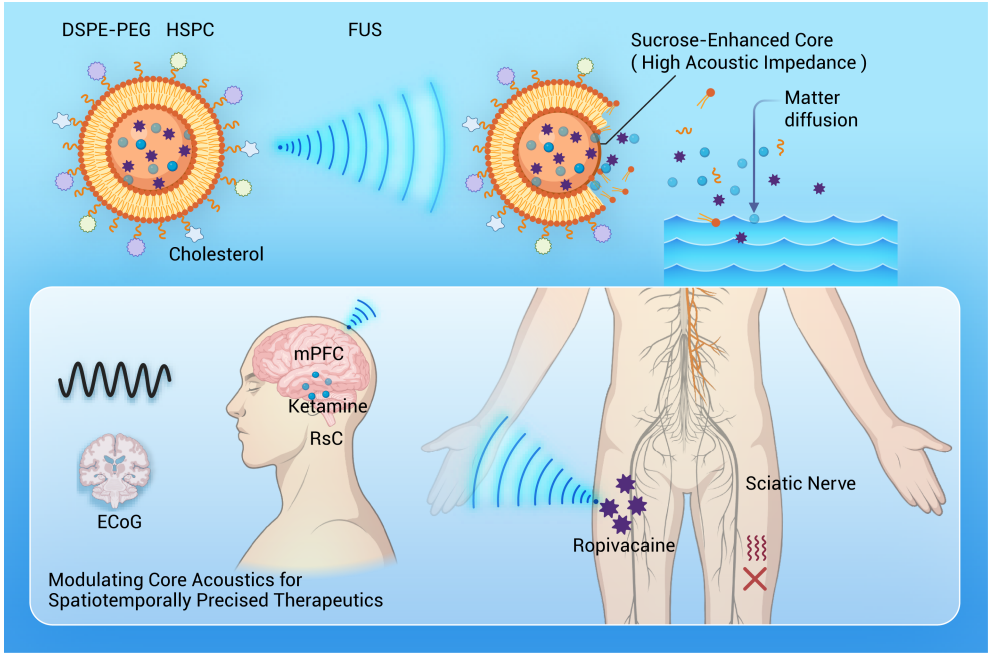

Figure 1. This schematic diagram illustrates the working principle of AALs: after being activated by FUS AALs achieve spatiotemporally precise drug delivery by virtue of their sucrose-enhanced high acoustic impedance core, thereby enabling targeted neuromodulation of the central brain regions (mPFC and RsC) and the peripheral sciatic nerve. Abbreviation: HSPC, hydrogenated soybean phosphatidylcholine; FUS, focused ultrasound; mPFC, medial prefrontal cortex; RsC, retrosplenial cortex; ECoG, electrocorticography.

article will critically examine the scientific highlights of this study, objectively analyze the remaining challenges, and discuss future research directions.

CLARIFICATION OF SCIENTIFIC HIGHLIGHTS

Ingenious acoustic design and outstanding clinical translation potential

The central innovation of this work lies in its acoustic design philosophy. Instead of resorting to elaborate strategies that rely on gaseous cores or exotic materials, the authors simply added a small amount (5%) of sucrose to the liposomal inner buffer. This maneuver reproducibly elevates the acoustic impedance of the core medium from 1.55 to 1.60 MPa·s·m^{-1}, generating sufficient acoustic mismatch with the surrounding plasma. Consequently, incident ultrasound energy is efficiently converted into a transient increase in membrane permeability, which drives drug release. The formulation retains high colloidal stability in the absence of ultrasound (no changes in physicochemical parameters after 90 days at 4°C) yet enables rapid on-demand release under pulsed low-intensity ultrasound. Critically, all excipients including phospholipids, cholesterol, and sucrose, are compendial or GRAS, and the manufacturing protocol (thin-film hydration, extrusion, and tangential-flow filtration (TFF)) is already standard in industrial liposome production. This removes the most common roadblocks to swift clinical translation.

Well-defined mechanism: acoustic property dominance with safety risks averted

Through a set of elegant experiments, the authors ruled out significant contributions from thermal effects or inertial cavitation. Internal media exhibiting different acoustic impedances but identical osmolality (sucrose, glucose, NaCl) produced markedly different drug release efficiencies, and the release rate scaled tightly with the impedance mismatch. This finding provides compelling evidence that the change in core acoustic properties rather than osmotic pressure alone governs ultrasound responsiveness. Acoustic emission monitoring and *in vivo* blood-brain barrier integrity assays revealed no signatures of harmful inertial cavitation, and histological analyses confirmed that therapeutic-level ultrasound plus AALs induces no detectable damage in brain parenchyma or peripheral nerve tissue. This favorable safety profile is a prerequisite for applications in sensitive organs such as the brain.

Functional validation: precise, non-invasive neuromodulation in both central and peripheral nervous systems

(1) Central neuromodulation: Ketamine was selectively delivered to the mPFC (implicated in antidepressant-like effects) and RsC (linked to dissociative states). Solid-phase microextraction directly quantified tissue drug levels, revealing 5 mm spatial resolution and a twofold increase in ketamine concentration in the sonicated region versus the contralateral tissue. Electrocorticography (ECoG) and open-field behavior assays further demonstrated functional specificity: mPFC "uncaging" (drug release triggered by ultrasound) evoked a sustained gamma-band power surge and an anxiolytic-like increase in center-field exploration, whereas RsC uncaging produced distinct theta/alpha/beta band signatures. Thus, the divergent physiological actions of the same drug can be spatially decoupled, offering a new paradigm for precision psychiatry.

(2) Peripheral nerve block: AALs loaded with ropivacaine were sonicated over the sciatic nerve, producing a reversible (> 1 h) decrease in mechanical sensitivity (von Frey test) without ECoG abnormalities or histological damage. This establishes a fully non-invasive alternative to injectable local anesthesia for pain management.

CHALLENGES AND FUTURE PERSPECTIVES

Despite demonstrating superior targeted release performance in animal studies, the clinical translation of AALs faces multiple challenges, including approximately 10% baseline drug leakage, insufficient target site enrichment efficiency, potential toxicity due to easy clearance by the liver and spleen, and quality control difficulties in large-scale production. Additionally, their mechanism of action remains unclear, and long-term safety requires further validation. To advance clinical applications, future research will focus on four key directions: precise temporal control of drug release, validation of long-term biocompatibility and manufacturability, confirmation of efficacy in clinically relevant disease models, and integration of real-time monitoring technologies. To advance this technology, next-generation carrier designs need to be explored, including hybrid lipid-polymer membranes and stimulus-responsive core matrices. These designs would effectively reduce passive drug leakage under therapeutically applicable acoustic parameters while enhancing the efficiency of ultrasound-triggered release. In translational research, comprehensive toxicological analyses based on international regulatory standards are required, alongside the establishment of scalable production processes compliant with cGMP standards to ensure batch-to-batch consistency and product stability. Furthermore, rigorous evaluation in large animal models with clinical predictive value is essential to elucidate exposure-response relationships and define therapeutic windows for specific diseases. The development of imaging-capable liposomes, combined with real-time ultrasound monitoring and closed-loop feedback systems, represents a crucial step toward precision and image-guided drug delivery by integrating theranostic strategies. These collaborative efforts are poised to advance this highly promising technological platform toward clinical application, establishing it as a reliable tool for non-invasive neuromodulation and precision medicine.

CONCLUSION

In summary, the AALs developed by Purohit et al. achieved ultrasound-mediated precision drug delivery through innovative nanocarrier design. The fundamental mechanism involves the precise tuning of the liposomal core's acoustic impedance *via* biocompatible excipients (e.g., sucrose), thereby enabling efficient energy coupling with low-intensity pulsed ultrasound. Based on a mechanism of acoustic impedance mismatch, this approach enables on-demand drug release without dependence on inertial cavitation, gas bubbles, or significant thermal effects, thereby addressing critical safety and translatability limitations inherent in previous systems. Notably, while sucrose-containing AALs and sucrose-free control liposomes exhibited similar biodistribution patterns and accumulation at target sites, only AALs achieved highly efficient ultrasound-triggered drug release. This result confirms the platform's inherent targeting capability and validates its on-demand therapeutic function. Through the strategy of systemic administration and local activation, it has successfully achieved spatially precise pharmacological regulation of specific brain regions (such as the mPFC and RsC) and peripheral nerves. Compared to alternative delivery systems (such as polymer carriers), AALs offer distinct advantages through their exclusive use of clinically validated excipients and manufacturing processes, providing a clearer clinical translation pathway with lower risks. In summary, AALs provide a precise drug delivery platform that combines high efficiency, safety, and versatility, opening a practical pathway for tackling complex clinical challenges.

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FUNDING AND ACKNOWLEDGMENTS

The authors acknowledge the financial support from National Natural Science Foundation of China (52572305). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.