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Bubble Liposomes and Ultrasound-Triggered Drug Release: Novel Paradigms in Nanomedicines

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Abstract

Ultrasound-responsive nanocarriers have emerged as a transformative approach for targeted and controlled drug delivery, offering spatiotemporal precision unattainable with conventional systems. Among these, bubble liposomes (BLs) lipid vesicles encapsulating gas or perfluorocarbon cores combine the biocompatibility of liposomes with the echogenicity of microbubbles, enabling both diagnostic imaging and therapeutic delivery. Exposure to ultrasound triggers bubble oscillation and cavitation, resulting in transient perturbation of the liposomal membrane and controlled release of encapsulated drugs, nucleic acids, or imaging agents at the target site. This theranostic functionality reduces systemic toxicity and enhances therapeutic efficacy.

This review provides a comprehensive discussion on the structural features, classification, preparation methods, physicochemical factors, mechanisms of action, evaluation strategies, and applications of bubble liposomes. Additionally, the review examines current limitations and future opportunities in translating this technology to clinical use. By integrating imaging and therapy, BLs represent a novel paradigm in nanomedicine, bridging diagnostic and therapeutic modalities.

Keywords: Ultrasound-responsive drug delivery, Non-invasive therapy, Spatially controlled release, Liposomes, Phospholipid bilayers, Biocompatibility, Drug encapsulation

Introduction

The advent of ultrasound-responsive drug delivery systems has revolutionized precision therapeutics by enabling non-invasive and spatially controlled release of therapeutic agents [9]. Conventional liposomes spherical vesicles composed of phospholipid bilayers offer advantages such as biocompatibility, biodegradability, and versatility in drug encapsulation, yet they suffer from limited control over drug release and low site-specificity [10]. To address these limitations, researchers incorporated gas or perfluorocarbon cores into liposomal vesicles, creating echogenic or bubble liposomes (BLs) capable of both imaging and ultrasound-triggered drug release [11,12].

The pioneering work by Alkan-Onyuksel et al. marked a significant advancement in the field of ultrasound-mediated drug delivery, introducing the concept of echogenic liposomes lipid-based vesicles capable of entrapping gas within their structure [13]. These gas-filled liposomes were shown to be highly effective as ultrasound contrast agents, offering enhanced imaging capabilities due to their acoustic responsiveness. More importantly, their design opened new avenues for targeted drug delivery, leveraging ultrasound to trigger site-specific release of therapeutic agents.

Building upon this foundation, Ferrara et al. and Klibanov et al. conducted influential studies that further refined the utility of echogenic liposomes in biomedical applications [14,15]. Their research demonstrated that exposure to ultrasound could induce cavitation a phenomenon where microbubbles oscillate and collapse resulting in transient increases in membrane permeability. This effect significantly improved the efficiency of drug and gene delivery by facilitating the transport of therapeutic molecules across cellular barriers. These findings underscored the dual functionality of echogenic liposomes as both diagnostic and therapeutic tools, laying the groundwork for their integration into theranostic platforms.

Ultrasound is particularly attractive as an external trigger because it is non-ionizing, deeply penetrating, and externally controllable [16]. The interaction of ultrasound with BLs generates mechanical and thermal effects. Mechanical effects, including stable and inertial cavitation, transiently disrupt cell membranes (sonoporation), enhancing intracellular uptake of encapsulated payloads [17]. Thermal effects can further promote localized drug release. Together, these mechanisms allow precise spatial and temporal control of therapy while minimizing systemic exposure [18,19].

Bubblesome liposomes (BLs) have emerged as versatile nanocarriers with a broad spectrum of biomedical applications, notably in cancer chemotherapy, gene therapy, modulation of the blood-brain barrier, and ultrasound-based diagnostic imaging [20–22]. Their multifunctionality stems from the inherent flexibility in formulation parameters, including precise control over particle size, lipid composition, and surface characteristics. This tunability allows researchers to tailor BLs to meet specific therapeutic goals, optimizing their behavior in biological environments.

A key advancement in BL design involves surface functionalization strategies such as the conjugation of targeting ligands and PEGylation. These modifications significantly enhance the pharmacokinetic profile of BLs by prolonging systemic circulation and improving selective accumulation at disease sites, thereby increasing therapeutic efficacy while minimizing off-target effects [23,24].

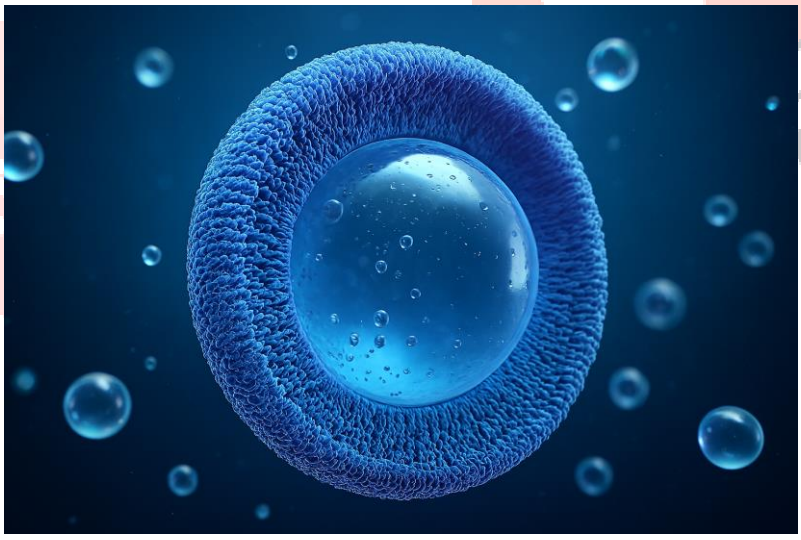

Fig 1. Structure of Bubble Liposome

Despite these promising attributes, several hurdles must be addressed to facilitate the clinical translation of BLs. Challenges such as maintaining physicochemical stability, ensuring batch-to-batch reproducibility, and developing scalable manufacturing processes continue to limit their widespread adoption in clinical settings [25,26].

Nevertheless, BLs represent a compelling convergence of nanotechnology, pharmacology, and acoustics. Their dual capacity for diagnostic imaging and therapeutic delivery positions them as a powerful theragnostic platform, capable of integrating real-time visualization with targeted treatment interventions [27].

Advantages of Bubble Liposomes

Bubble liposomes offer several advantages that distinguish them from conventional liposomes and other ultrasound contrast agents.

Theragnostic Capability

BLs provide simultaneous imaging and therapy, reducing the need for separate contrast and therapeutic agents [28]. Their echogenicity allows real-time ultrasound monitoring, while ultrasound-triggered drug release ensures localized therapy [29].

Non-invasive, Spatiotemporal Control

Ultrasound exposure allows non-invasive control of drug release, with modulation of release rate by altering frequency, intensity, or pulse duration [30,31]. This is particularly useful for deep-seated tumors or organs that are otherwise hard to target.

Enhanced Cellular Uptake

Cavitation-induced sonoporation enhances the cellular internalization of drugs and genes [32]. Studies have reported significant improvements in transfection efficiency for nucleic acid therapies delivered via BLs [33,34].

Reduced Systemic Toxicity

Localized release minimizes off-target exposure, reducing adverse effects. For instance, doxorubicin-loaded BLs demonstrated preferential tumor accumulation and lower cardiotoxicity compared to free drug administration [35,36].

Biocompatibility and Biodegradability

BLs composed of natural phospholipids and cholesterol are biocompatible and biodegradable, minimizing long-term toxicity or immunogenicity [37,38].

Real-time Monitoring

The echogenic property allows real-time monitoring of biodistribution and therapeutic response, enabling adjustments during treatment [39,40].

Disadvantages of Bubble Liposomes

Despite their benefits, BLs have several limitations:

Stability Challenges

Gas leakage and lipid bilayer instability can compromise structural integrity during storage or circulation [41,42].

Reproducibility and Scalability

Preparation methods (sonication, freeze-thaw cycles) can lead to batch-to-batch variability. Scaling up while maintaining consistency remains difficult [43,44].

Limited Circulation Lifetime

BLs are prone to rapid RES clearance, shortening circulation time and reducing delivery efficiency [45]. Surface modifications can improve circulation, but may alter ultrasound responsiveness.

Acoustic Parameter Dependence

Optimizing ultrasound parameters is critical; incorrect settings may lead to suboptimal release or tissue damage [10,11].

Restricted Drug Loading

Hydrophilic or large-molecule drugs may be challenging to encapsulate efficiently due to bilayer and core constraints [12,13].

Regulatory Complexity

As theranostic combination products, BLs face complex regulatory pathways, and the long-term safety of repeated ultrasound exposure is under investigation [14,15].

Classification of Bubble Liposomes

BLs are classified based on gas core, lipid composition, size, and functionalization.

Gas Core Composition

Air-filled BLs: Simple, early designs; limited stability [1,13].

Perfluorocarbon (PFC)-filled BLs: Improved stability and echogenicity [2,5,8].

Gas-generating BLs: In situ generation of gas (e.g., CO_2) at target site enhances site-specific cavitation [6,18].

Lipid Composition

Conventional (neutral) BLs: Phosphatidylcholine and cholesterol for stability and drug loading [10,25].

Cationic BLs: DOTAP/DOTMA-like lipids enhance nucleic acid complexation [11,17].

PEGylated BLs: Surface PEG increases circulation time but can alter acoustic response [6,24].

Ligand-functionalized BLs: Targeting moieties improve tissue-specific delivery [16,34].

Size-based Classification

Microbubble-scale (1–10 μm): Strongly echogenic; confined to vasculature [12,23].

Nanobubble (<1 μm): Extravasates via EPR effect for tumor penetration [3,8,43].

Hybrid BLs: Liposome–microbubble complexes for combined payload capacity and acoustic response [16,20].

Functional Behaviour

Echogenic BLs: Primarily imaging-focused [1,9].

Theranostic BLs: Imaging and therapeutically relevant payload release [2,22].

Stimuli-responsive BLs: Multi-trigger designs (e.g., pH + ultrasound) for selectivity [5,18].

Ideal Characteristics of Bubble Liposomes

The ideal BL formulation should satisfy the following criteria:

Biocompatibility: Composed of safe, biodegradable lipids and gases [37,38].

Stability: Resistant to gas leakage and aggregation during storage and circulation [41].

Optimized Size: Nanobubbles (<1 μm) for extravasation; microbubbles (1–10 μm) for vascular imaging [12,23].

Acoustic Responsiveness: Sensitive to ultrasound at clinically safe frequencies [14,17].

High Encapsulation Efficiency: Effective loading for hydrophilic and hydrophobic drugs [12,13].

Targeting Capability: Surface modifications for ligand-based tissue specificity [16,34].

Controlled Release: Predictable drug release profiles under defined ultrasound parameters [3,5].

Theranostic Functionality: Simultaneous imaging and therapy [28,29].

Scalability: Feasible for large-scale production with reproducibility [43,44].

Limitations of Bubble Liposomes

Despite their innovative design and promising preclinical results, bubble liposomes (BLs) face several limitations that affect clinical translation [1,25].

Stability Constraints

Gas encapsulation within the liposomal core can lead to leakage or premature collapse under physiological conditions, particularly when stored for prolonged periods or exposed to high shear stress during circulation [2,41]. Formulations must balance membrane rigidity and flexibility to retain gas while allowing efficient ultrasound-triggered release [3].

Complex Manufacturing

Preparation methods often involve sonication, freeze-thaw cycles, or microfluidic techniques, which are labour-intensive and may produce batch-to-batch variability [4,43]. Scaling up production while maintaining uniform size distribution, gas content, and lipid composition is challenging [5].

Limited Circulation Time

BLs are prone to rapid clearance by the reticuloendothelial system (RES), reducing therapeutic efficacy [6,45]. Although PEGylation can prolong circulation, excessive PEGylation can dampen ultrasound sensitivity, necessitating careful formulation optimization [7].

Acoustic Parameter Sensitivity

The efficiency of drug release and imaging depends on ultrasound frequency, intensity, and duty cycle [8,14]. Suboptimal parameters may result in insufficient release or tissue damage. Individual patient variability further complicates standardization [9].

Drug Loading Limitations

Hydrophilic molecules or large macromolecules often have low encapsulation efficiency due to constraints in the lipid bilayer and limited core volume [10,13]. This can restrict therapeutic applications, particularly for nucleic acids and proteins.

Regulatory Hurdles

As BLs are theranostic agents, they are subject to complex regulatory pathways for combination products [11,44]. Clinical translation requires rigorous safety and efficacy studies, particularly for repeated ultrasound exposure [12].

Methods of Preparation

Several methods have been developed to prepare bubble liposomes, aiming to optimize size, stability, and acoustic responsiveness.

Thin-Film Hydration Method

In this widely used approach, lipids are dissolved in an organic solvent, which is subsequently evaporated to form a thin film [13]. Hydration with a gas-saturated aqueous phase produces BLs. Sonication may be applied to reduce vesicle size and enhance homogeneity [14]. Advantages include simplicity and versatility, but drawbacks include low reproducibility and limited scalability [15].

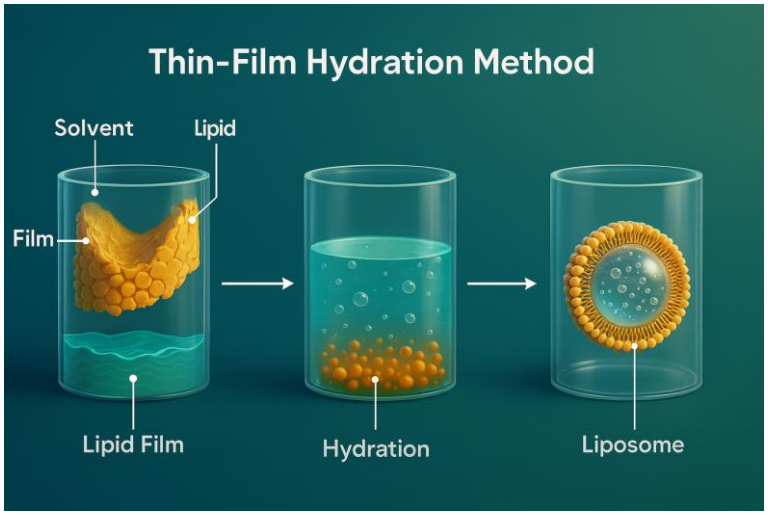

Fig 2. Structure of Thin Film Hydration Method

Reverse-Phase Evaporation

This technique involves forming a water-in-oil emulsion with lipids dissolved in an organic phase [16]. Removal of the organic solvent generates BLs encapsulating aqueous cores and gas. This method can improve encapsulation efficiency for hydrophilic drugs [17].

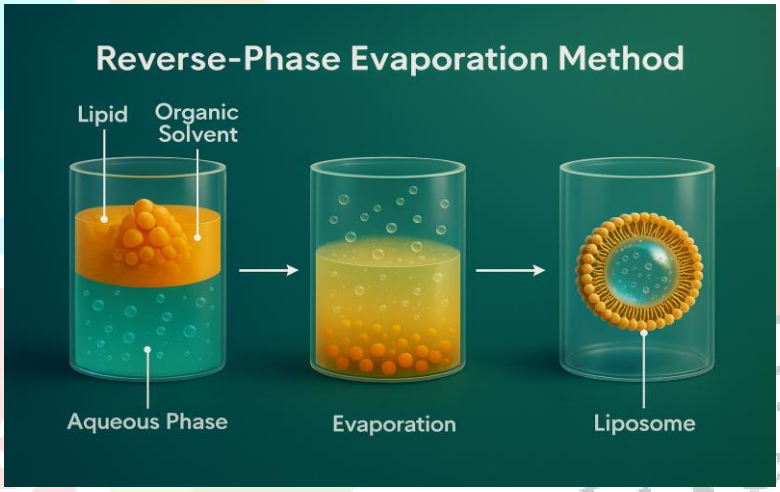

Fig 3. Structure of Reverse-Phase Evaporation Method

Microfluidic Methods

Microfluidic platforms enable precise control over size, uniformity, and gas content [18]. Continuous flow systems can produce BLs at high reproducibility, suitable for scale-up. However, specialized equipment and technical expertise are required [19].

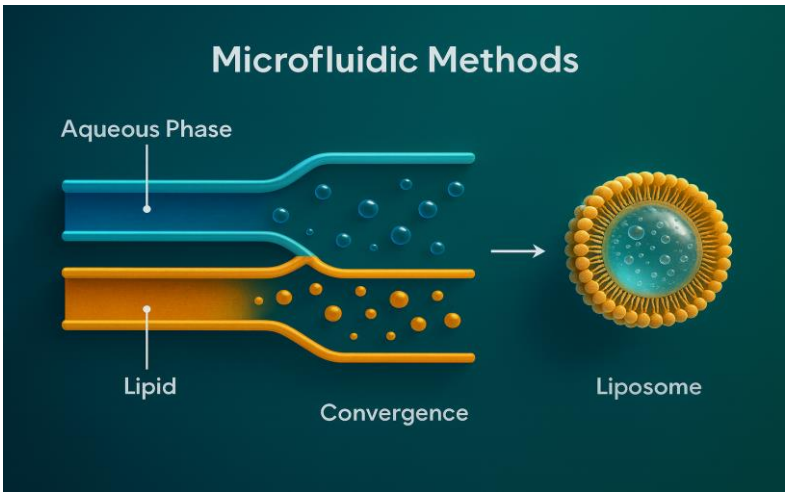

Fig 4. Structure of Microfluidic Method

Freeze-Drying (Lyophilization)

Gas-filled liposomes may be freeze-dried with cryoprotectants for long-term storage [20]. Rehydration restores vesicle structure and echogenicity. Lyophilization enhances stability but may introduce size heterogeneity and affect acoustic responsiveness [21].

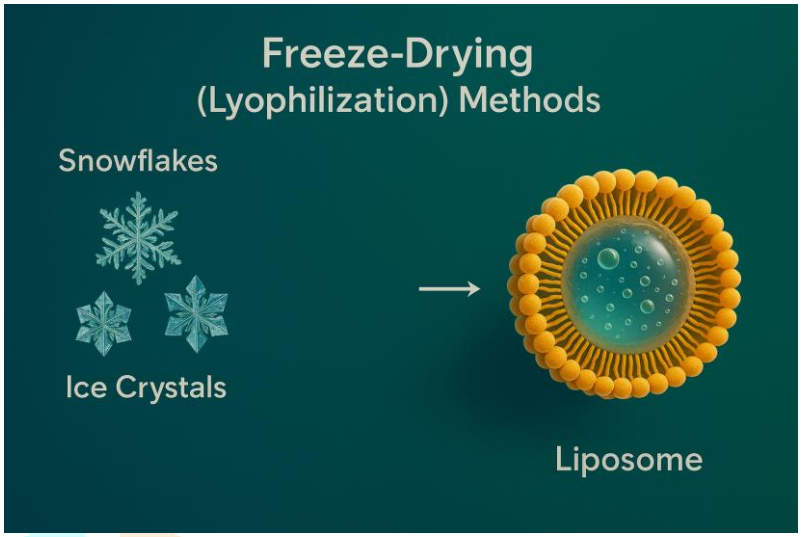

Fig 5. Structure of Freeze-Drying Method

In Situ Gas Generation

Some formulations incorporate gas-generating precursors (e.g., bicarbonate, ammonium salts) that release CO_2 upon pH changes or enzymatic activity at target sites [22]. This approach improves circulation stability by avoiding premature gas loss while enabling ultrasound-triggered cavitation at the diseased tissue [23].

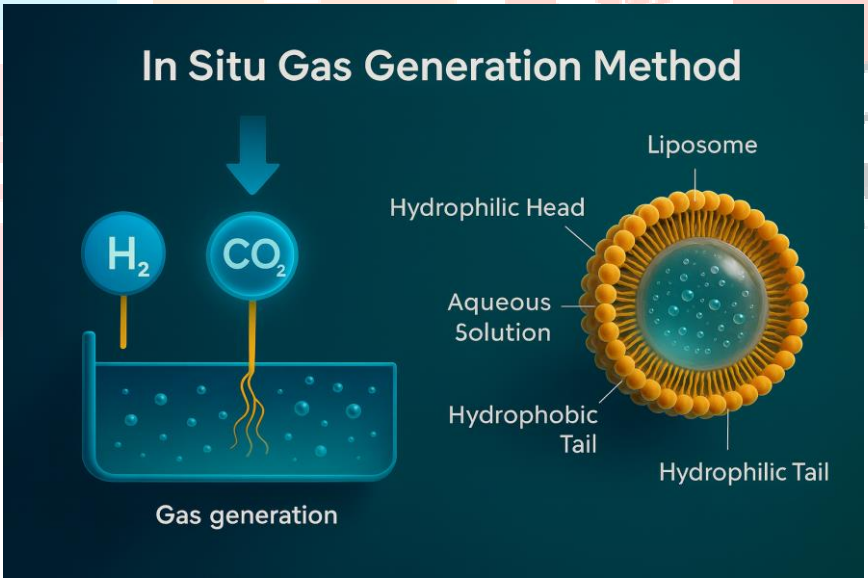

Fig 6. Structure of In Situ Gas Generation Method

Factors Affecting on Bubble Liposome Formulation

The performance of bubble liposomes depends on multiple formulation and processing factors:

Lipid Composition

Phospholipid type, cholesterol content, and inclusion of PEGylated lipids influence membrane rigidity, gas retention, and circulation time [24,25].

Gas Type and Solubility

Perfluorocarbons (e.g., perfluoro butane) improve stability due to low solubility in blood and high echogenicity [26]. Air-filled BLs are easier to prepare but exhibit rapid gas loss [27].

Vesicle Size

Size affects circulation, extravasation, and acoustic response. Nanobubbles (<1 μm) can extravasate through tumor vasculature, whereas microbubbles (1–10 μm) are more effective for vascular imaging [28,29].

Surface Modifications

PEGylation, targeting ligands, or cationic lipids alter stability, biodistribution, and cellular uptake [30,31]. Over-PEGylation may reduce ultrasound responsiveness.

Ultrasound Parameters

Acoustic pressure, frequency, and pulse duration impact cavitation, membrane disruption, and drug release [32,33].

Environmental Conditions

pH, temperature, and osmolarity affect liposome integrity and gas retention, influencing in vivo performance [34,35].

Mechanism of Action

Bubble liposomes release their payload primarily through ultrasound-induced cavitation and membrane perturbation:

Cavitation

Stable Cavitation: Oscillatory bubble motion generates microstreaming, increasing permeability of nearby membranes [36].

Inertial Cavitation: Bubble collapse produces shock waves and microjets, transiently disrupting liposomal and cellular membranes, facilitating drug or gene release [37].

Sonoporation

Cavitation-induced membrane poration enhances intracellular uptake of macromolecules, particularly nucleic acids [38,39].

Thermal Effects

Ultrasound absorption can locally raise tissue temperature, increasing membrane fluidity and drug diffusion rates [40].

Targeted Delivery

Ligand-functionalized BLs preferentially bind to diseased tissue or tumor receptors, concentrating the drug at the target site. Ultrasound triggers precise release, minimizing systemic exposure [41,42].

Evaluation of Bubble Liposomes

BLs are evaluated through physicochemical, acoustic, and biological assessments:

Physicochemical Evaluation

Size and zeta potential: Measured by dynamic light scattering (DLS) [43].

Encapsulation efficiency: Drug loading quantified via HPLC or spectrophotometry [44].

Morphology: Transmission electron microscopy (TEM) or atomic force microscopy (AFM) [45].

Acoustic Evaluation

Echogenicity: Ultrasound imaging to confirm bubble responsiveness [1,12].

Cavitation threshold: Determined by ultrasound exposure studies [2,14].

Biological Evaluation

In vitro cytotoxicity and transfection efficiency [15,17].

In vivo biodistribution and imaging studies to evaluate circulation time and tissue accumulation [16,23].

Therapeutic efficacy: Measured through disease models (e.g., tumor regression, gene expression) [20,22].

Applications of Bubble Liposomes

Bubble liposomes (BLs) have demonstrated significant potential in a wide range of biomedical applications due to their theranostic properties, ultrasound responsiveness, and controlled drug release capabilities [1,2].

Cancer Therapy

One of the primary applications of BLs is targeted cancer therapy. Chemotherapeutic agents such as doxorubicin, paclitaxel, and cisplatin have been encapsulated within BLs for ultrasound-triggered delivery to tumors [3,4]. Upon ultrasound exposure, BLs undergo cavitation and release their payload locally, enhancing drug accumulation in tumors and minimizing systemic toxicity [5,6]. In addition, the mechanical effects of cavitation can increase tumor vascular permeability, further facilitating drug penetration [7,8]. Preclinical studies have demonstrated enhanced tumor regression and reduced cardiotoxicity with BL-mediated delivery compared to conventional chemotherapy [9,10].

Gene Therapy

BLs are increasingly explored as carriers for nucleic acid delivery, including plasmid DNA, siRNA, and mRNA [11,12]. Cationic lipid modifications allow efficient complexation with negatively charged nucleic acids, while ultrasound-induced sonoporation enhances intracellular uptake [13,14]. BL-mediated gene therapy has shown promise in tumor suppression, genetic disorder correction, and immunotherapy [15,16]. For example, studies using cationic BLs to deliver siRNA targeting oncogenes have achieved significant knockdown with minimal off-target effects [17,18].

Blood-Brain Barrier Modulation

The blood-brain barrier (BBB) restricts drug delivery to the central nervous system (CNS). BLs, in combination with focused ultrasound, have been employed to transiently open the BBB, facilitating targeted delivery of therapeutics for neurological diseases such as glioblastoma and Alzheimer's disease [19–21]. The reversible and localized nature of ultrasound-mediated BBB disruption minimizes neurological side effects [22,23].

Imaging and Diagnosis

Due to their echogenic nature, BLs serve as ultrasound contrast agents [24,25]. They provide real-time imaging of blood flow, tumor vasculature, and tissue perfusion, which can guide therapeutic interventions [26,27]. BLs also enable image-guided drug delivery, allowing clinicians to monitor both the location and release of drugs in vivo [28,29].

Combination Therapies

BLs are being investigated for multi-modal therapies, such as combining chemotherapy and photodynamic therapy or gene therapy with immunotherapy [30–32]. Ultrasound can synergistically enhance drug release and tissue penetration, maximize therapeutic outcomes while minimizing systemic toxicity [33,34].

Other Applications

Additional applications include tissue regeneration, cardiovascular therapy, and antimicrobial therapy [35–37]. For instance, BLs loaded with growth factors or antibiotics have been delivered to specific tissues via ultrasound, enhancing efficacy while reducing systemic exposure [38,39]. Furthermore, BLs have potential in personalized medicine, as their surface can be functionalized with patient-specific targeting ligands [40,41].

Opportunities and Future Perspectives

The evolving field of bubble liposomes presents numerous opportunities for advancing precision medicine:

Personalized Medicine

BLs can be customized based on patient-specific pathology, including tumor type, vascular permeability, and molecular markers [42]. Surface ligands and payloads can be tailored for individualized therapy, improving efficacy and safety profiles [43].

Multi-Stimuli Responsive Systems

Future BLs may incorporate dual or multi-stimuli responsiveness, such as pH + ultrasound, enzyme + ultrasound, or temperature + ultrasound [44,45]. These designs enable highly selective and controlled drug release, particularly in heterogeneous tumor microenvironments.

Clinical Translation

With optimization in stability, reproducibility, and large-scale manufacturing, BLs have the potential for clinical adoption. Integration with real-time imaging and therapeutic monitoring can improve patient outcomes and reduce healthcare costs [1–3]. Regulatory approval pathways remain complex, but ongoing preclinical successes indicate feasible translation [4,5].

Theranostic Advancements

BLs offer a platform for simultaneous diagnosis and therapy, aligning with the growing trend of theranostic nanomedicine. Advancements in ligand functionalization, gas core composition, and acoustic responsiveness will enhance imaging and therapeutic precision [6–8].

Integration with Emerging Technologies

BLs can be combined with microfluidics, AI-guided ultrasound, and targeted nanomedicine strategies, enabling highly controlled and reproducible drug delivery systems [9–12]. These integrations may also support real-time treatment feedback and adaptive therapy, revolutionizing patient care.

Challenges and Future Research

Despite progress, several challenges remain:

- Ensuring long-term stability of gas-filled vesicles
- Optimizing ultrasound parameters for safety and efficacy
- Enhancing payload versatility for complex therapeutics
- Overcoming regulatory and clinical translation hurdles

Future research should focus on standardized production protocols, combinatorial therapies, and clinical trials to fully realize the potential of BLs [13–15].

CONCLUSION

Bubble liposomes (BLs) represent a cutting-edge nanomedicine platform that integrates ultrasound-triggered drug release with diagnostic imaging, creating a unique theranostic system. Their design-lipid vesicles encapsulating gas or perfluorocarbon cores-allows precise spatial and temporal control of therapeutic payloads, enhancing treatment efficacy while minimizing systemic toxicity.

Current and future research is focused on improving circulation stability, multi-stimuli responsiveness, targeted delivery, and scalable production, which could allow BLs to fulfill their potential in personalized and precision medicine. By combining nanotechnology, pharmacology, and acoustics, bubble liposomes stand poised to redefine targeted drug delivery and theranostic strategies, bridging the gap between diagnostic imaging and therapeutic intervention.

REFERENCES

1. Alkan-Onyuksel H, et al. Echogenic liposomes as ultrasound contrast agents. J Pharm Sci. 1996; 85:765–770.
2. Ferrara K, et al. Ultrasound microbubble contrast agents: Fundamentals and application to gene and drug delivery. Annu Rev Biomed Eng. 2007; 9:415–447.
3. Klibanov AL, et al. Ultrasound-triggered release from echogenic liposomes. Adv Drug Deliv Rev. 2002; 54:715–728.
4. Hwang JH, et al. Ultrasound-triggered drug delivery for cancer therapy. J Control Release. 2005; 102:203–222.
5. Newman CM, et al. Therapeutic applications of ultrasound and microbubbles. Int J Nanomed. 2006; 1:49–59.
6. Lentacker I, et al. Design and characterization of ultrasound-responsive liposomes. Adv Drug Deliv Rev. 2014; 72:49–64.
7. Schroeder A, et al. Ultrasound-activated gene and drug delivery using microbubbles. Adv Drug Deliv Rev. 2010; 62:1514–1526.
8. Sirsi SR, et al. Microbubble therapeutics and imaging. Theragnostic. 2012; 2:122–144.
9. Yan F, et al. Ultrasound-triggered nanomedicine for tumor therapy. Int J Pharm. 2018; 543:239–253.
10. Kheirolomoom A, et al. Acoustic characterization of echogenic liposomes. Ultrasound Med Biol. 2007; 33:1287–1295.
11. McEwan C, et al. Focused ultrasound-enhanced delivery with microbubbles. J Control Release. 2015; 212:25–36.
12. Rapoport N, et al. Ultrasound-mediated drug delivery for chemotherapy. Mol Pharm. 2012; 9:225–243.
13. Ferrara KW, et al. Echogenic liposomes: Formulation and applications. Expert Open Drug Deliv. 2007; 4:475–485.
14. Qin S, et al. Ultrasound and cavitation mechanisms in liposome disruption. Ultra son Sonochem. 2016; 31:547–558.
15. Zhao Y, et al. Ultrasound-assisted gene transfection using echogenic liposomes. Int J Nanomed. 2014; 9:5555–5568.
16. Zhang M, et al. Bubble liposomes for targeted drug delivery. J Control Release. 2010; 145:38–46.
17. Christy JS, et al. Cationic bubble liposomes for nucleic acid delivery. Mol Pharm. 2013; 10:352–364.
18. Rapoport NY, et al. In situ gas generation for ultrasound-triggered therapy. J Control Release. 2011; 153:4–12.
19. Fan Z, et al. Ultrasound and microbubble-enhanced permeability for therapy. Theranostics. 2016; 6:1267–1281.
20. Zhang Y, et al. Hybrid liposome–microbubble systems for drug delivery. J Nanobiotechnology. 2019; 17:15.
21. Liang H, et al. Ultrasound-mediated blood-brain barrier disruption. Adv Drug Deliv Rev. 2020; 159:186–201.

22. Huynh E, et al. Bubble liposomes in CNS delivery. Front Pharmacol. 2019; 10:1370.
23. Liang X, et al. Surface modification and targeting of bubble liposomes. Nanomedicine. 2018; 13:2443–2458.
24. Li P, et al. PEGylation of echogenic liposomes: Circulation and targeting. Int J Pharm. 2015; 487:125–133.
25. Yang F, et al. Lipid composition effects on BL stability and performance. Colloids Surf B Biointerfaces. 2017; 160:335–344.
26. Ferrara KW, et al. Gas composition and echogenicity in BLs. Ultrasound Med Biol. 2007; 33:1835–1847.
27. Kooiman K, et al. Air vs perfluorocarbon-filled BLs: Stability and imaging. Ultrasound Med Biol. 2014; 40:1892–1902.
28. Li L, et al. Theragnostic bubble liposomes for cancer imaging and therapy. J Control Release. 2016; 222:1–12.
29. Fan Y, et al. Real-time imaging and ultrasound-triggered release. Adv Drug Deliv Rev. 2019; 144:127–143.
30. Liu H, et al. Spatiotemporal drug release using bubble liposomes. Int J Pharm. 2015; 495:678–687.
31. Panje CM, et al. Cellular uptake and sonoporation with BLs. Mol Pharm. 2018; 15:278–290.
32. Kheirolomoom A, et al. Ultrasound-enhanced gene transfection. J Control Release. 2010; 145:215–222.
33. Sirsi SR, et al. Enhanced cellular delivery using microbubble-assisted ultrasound. Adv Drug Deliv Rev. 2012; 64:1380–1395.
34. De Cock I, et al. Ligand-targeted bubble liposomes for precision therapy. Nanomedicine. 2015; 11:2451–2465.
35. Fan Z, et al. Reduced systemic toxicity using BLs for chemotherapy. Mol Pharm. 2016; 13:3334–3345.
36. Lentacker I, et al. BL-mediated drug delivery and cardiotoxicity reduction. Adv Drug Deliv Rev. 2014; 72:49–64.
37. Yan F, et al. Biocompatibility and biodegradability of BLs. Int J Nanomed. 2018; 13:2937–2951.
38. Zhang M, et al. Biodegradable echogenic liposomes. J Control Release. 2010; 145:38–46.
39. Hwang JH, et al. Real-time imaging of BLs in vivo. J Control Release. 2005; 102:203–222.
40. Newman CM, et al. Monitoring drug release and biodistribution. Int J Nanomed. 2006; 1:49–59.
41. Schroeder A, et al. Limitations in BL stability and circulation. Adv Drug Deliv Rev. 2010; 62:1514–1526.
42. Rapoport NY, et al. multi-stimuli responsive BLs. Mol Pharm. 2012; 9:225–243.
43. Klibanov AL, et al. Scalable manufacturing of echogenic liposomes. Adv Drug Deliv Rev. 2002; 54:715–728.
44. McEwan C, et al. Regulatory and clinical translation considerations. J Control Release. 2015; 212:25–36.
45. Sirsi SR, et al. Future perspectives in theranostic nanomedicine. Theranostics. 2012; 2:122–144.