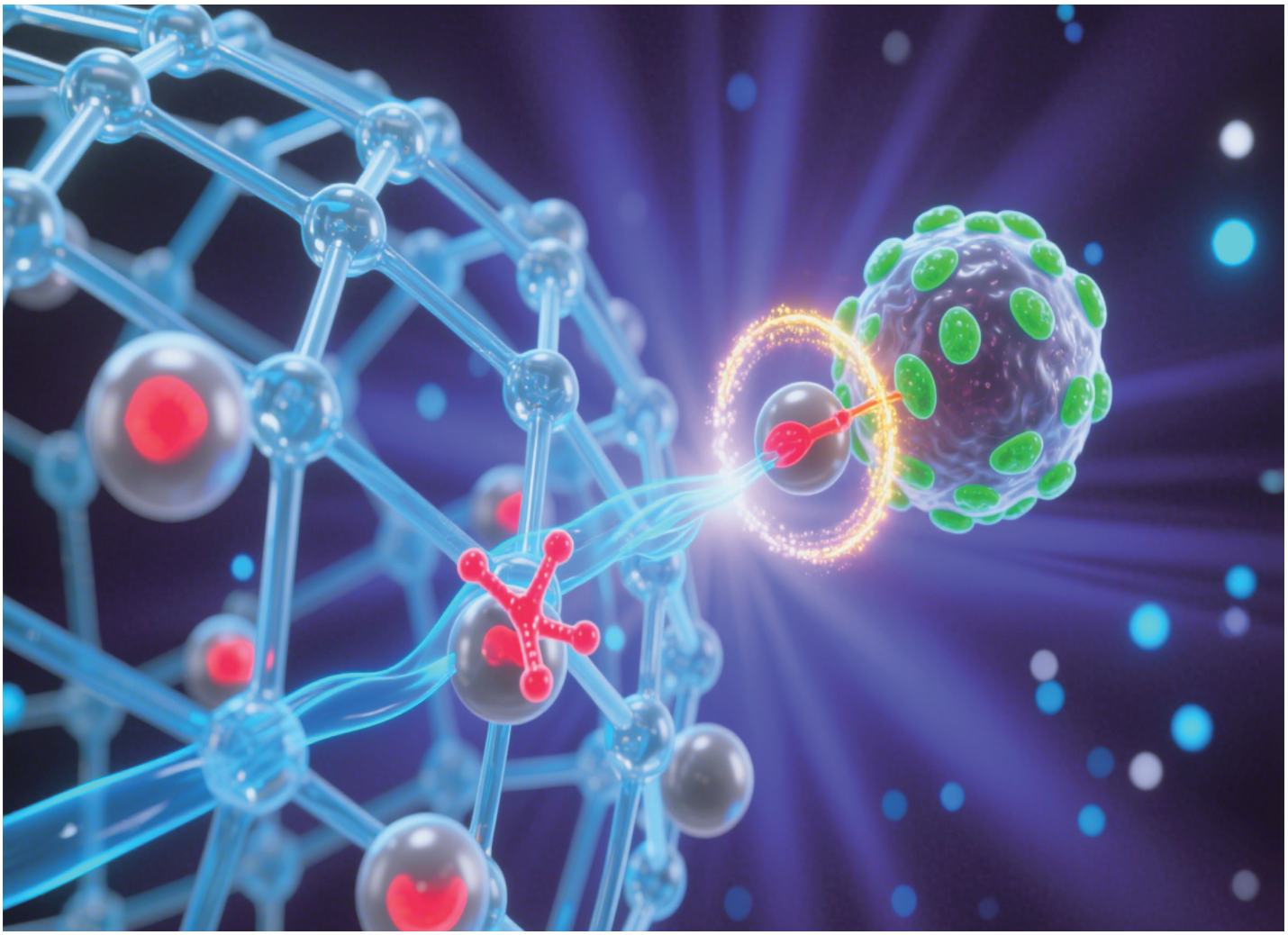

Showcasing research from Professor Xiuwen Wu's laboratory, Research Institute of General Surgery, Jinling Hospital, Affiliated to Nanjing University of Chinese Medicine, China

Advances in drug delivery systems based on liposome-composite hydrogel microspheres

This review summarizes advances in liposome-composite hydrogel microspheres (LHMs) for drug delivery, covering preparation methods, optimization, applications, and challenges. LHMs combine liposome and hydrogel advantages, offering biosafety, modifiability, controlled release, and targeting, with potential in drug delivery.

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Advances in drug delivery systems based on liposome-composite hydrogel microspheres

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Research on liposome-composite hydrogel microspheres (LHMs) drug delivery systems, primarily composed of drugs, liposomes, and hydrogels, has garnered growing scientific interest. LHMs exhibit biosafety, modifiability, a wide range of loaded drug categories (water-soluble or fat-soluble), controlled and sustainable drug release capability, and specific cell-targeted performance, which compensate for the shortcomings of conventional drug delivery methods due to the complementary advantages of liposome and hydrogel microspheres. In this review, we systematically analyze the existing literature on LHMs and provide a comprehensive overview of their preparation methods. Specifically, we detail the fabrication techniques for liposomes, including thin-film hydration, solvent injection, multiple emulsion, reverse-phase evaporation, gradient, freeze-drying, supercritical fluid, and microfluidic approaches as well as methodologies for LHMs, such as microfluidics, electrospraying, 3D printing, reverse-phase microemulsion, and physical adsorption. We also summarize the optimization approaches for LHMs properties when combining liposomes and hydrogel microspheres. Finally, we present the applications and challenges of LHMs. We hope that this review will foster more insights into LHMs in drug delivery fields.

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1. Introduction

To address the inherent limitations of conventional drugs, various drug delivery systems have been developed.[1–3] Despite these advancements, conventional drug delivery systems still encounter persistent challenges, such as the need to mitigate drug toxicity, prolong therapeutic efficacy, reduce dosing frequency, and enhance patient compliance.[4–6] With continuous research on nanocomposite drug delivery systems, many limitations of drugs have been solved while providing some novel functions to the delivery systems.

In 1965, Bangham *et al.* pioneered the dispersion of phospholipids in water, leading to the discovery of spherical structures observed under electron microscopy, which were termed "liposomes". These structures primarily consist of a phospholipid bilayer forming spherical vesicles with an aqueous core.[7] The amphiphilic nature of liposomes, arising from the hydrophilic head and hydrophobic tail of phospholipid molecules, enables the encapsulation of hydrophilic drugs within the aqueous core and lipid-soluble drugs within the bilayer.[8] Despite their ability to encapsulate drugs and address certain pharmaceutical limitations, liposomes exhibit inherent drawbacks, such as the cytotoxicity of positively charged liposomes, rapid hepatic clearance, susceptibility to digestive enzymes, and instability.[9,10] These limitations have hindered the advancement of liposome-based drug delivery systems, prompting increasing research interest in the development of liposome-composite hydrogel delivery systems as a potential solution.

Hydrogels are three-dimensional polymeric networks characterized by their biodegradability and hydrophilicity. These materials exhibit exceptional water absorption and retention capacities, closely mimicking the natural extracellular matrix, thereby facilitating cellular growth and promoting the regeneration of damaged tissues.[11,12] Notably, their excellent biocompatibility and resistance to enzymatic degradation make them an optimal choice for gastrointestinal tract repair.[13] The tunable porous structure of hydrogels provides a stable matrix for drug or cell encapsulation, effectively preventing rapid metabolic breakdown while enabling sustained and controlled release.[14] Furthermore, the remarkable plasticity of hydrogels enables their application in advanced fabrication techniques, including three-dimensional (3D)/four-dimensional (4D) printing,[15] microfluidics, and electrospinning into nano-microspheres.[16] This versatility, combined with their intrinsic biomimetic properties, underscores their potential as a multifunctional platform for tissue engineering and drug delivery systems.

Drug delivery systems integrating liposomes with hydrogels have garnered significant attention owing to their unparalleled

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and synergistic properties.[3,17] This review focuses on recent advancements in LHMs drug delivery systems, which incorporate liposomes, hydrogels, and encapsulated therapeutic agents.[17,18] Although liposomes offer substantial advantages as drug carriers, their inherent limitations, including rapid metabolic clearance *in vivo* and suboptimal stability *in vitro*, remain significant challenges.[19,20] In LHMs, hydrogels effectively address these limitations by enhancing stability and prolonging drug release, thereby expanding the therapeutic applications of liposomes while introducing novel functionalities.

LHMs demonstrate significant potential for diverse applications in medicine and biotechnology, offering substantial value in both research and clinical practice.[21,22] In this review, we systematically summarize the preparation methodologies of liposomes and LHMs, their performance optimization strategies, and their associated applications (Fig. 1A–D). Furthermore, we critically examine the current challenges and future perspectives of this advanced drug delivery system.

2. Preparation of liposomes and LHMs

2.1 Preparation of liposomes

Liposomes are vesicular structures formed through the hydration of phospholipid molecules, which self-assemble in an aqueous phase to create bilayer structures.[23–25] Liposomes are

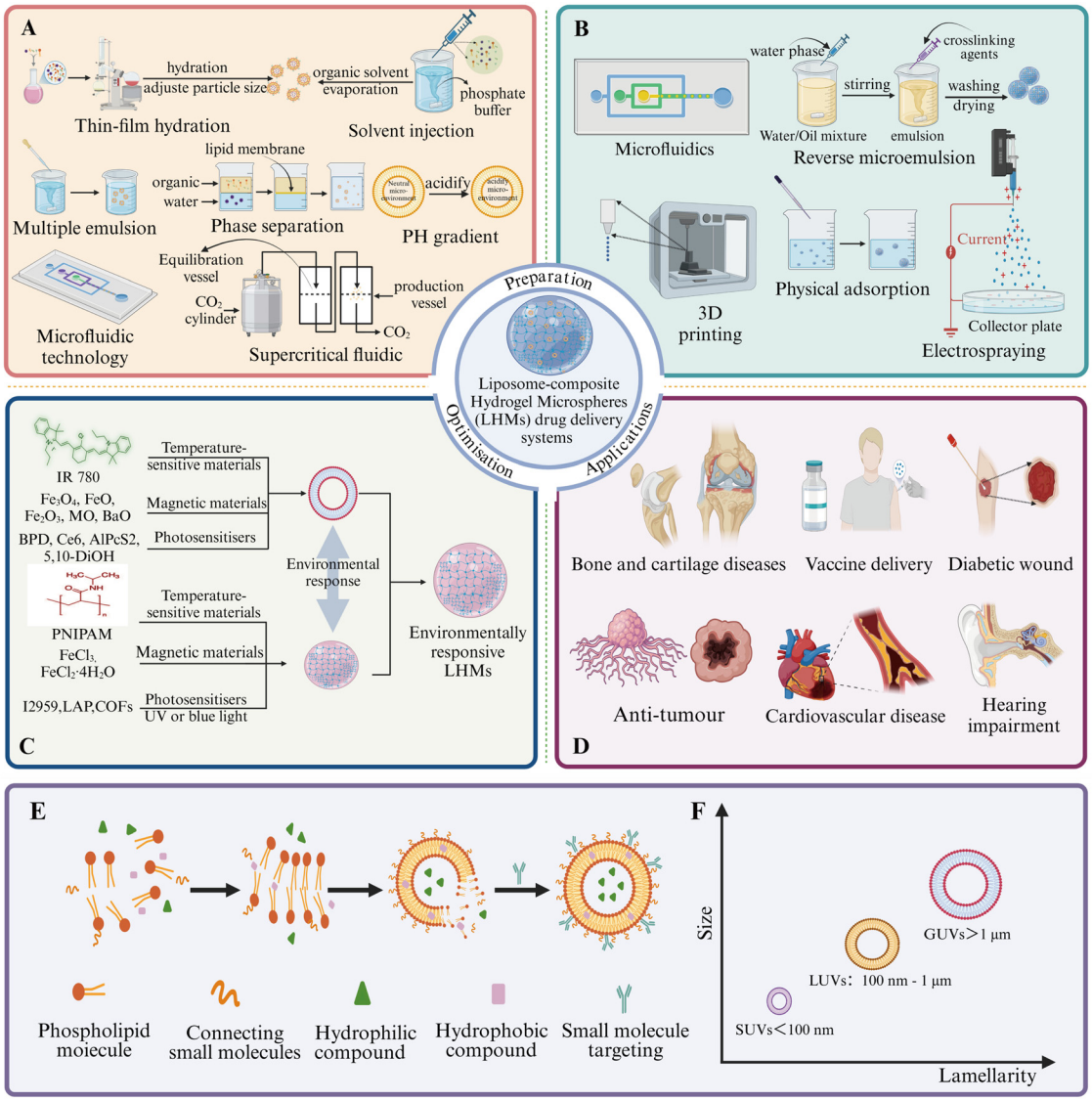

Fig. 1 Schematic of the preparation methodology, optimization process, and applications of LHMs as drug delivery systems. (A) Methods for liposome preparation. (B) Construction of LHMs drug delivery systems. (C) Optimization of liposomal and hydrogel components in LHMs utilizing environmentally responsive materials. (D) Therapeutic applications of LHMs in preclinical disease models. (E) Formation process of unicompartmental liposomes, including drug loading, small molecule-mediated targeted modification, and their fundamental structures. (F) Classification of unilamellar liposomes. IR 780, IR-780 iodide; COFs, covalent organic frameworks; LAP, lithium phenyl(2,4,6-trimethylbenzoyl)phosphinate; PNIPAM, poly(*N*-isopropylacrylamide); LHMs, liposome-composite hydrogel microspheres; SUVs, small unilamellar vesicles; LUVs, large unilamellar vesicles; GUVs, giant unilamellar vesicles. Created using Biorender.com.

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classified into unilamellar and multilamellar vesicles based on the number of lipid bilayers and the presence of a shared aqueous core. Unilamellar vesicles, also known as single-compartment liposomes, consist of a single phospholipid bilayer that encapsulates an aqueous core. Their formation and modification processes are schematically illustrated in Fig. 1E. These unilamellar systems are further subdivided into three categories based on size: (i) small unilamellar vesicles (SUVs, <100 nm), commonly referred to as nanoliposomes; (ii) large unilamellar vesicles (LUVs, 100 nm–1 μm); and (iii) giant unilamellar vesicles (GUVs, >1 μm), as shown in Fig. 1F. Multilamellar vesicles (MLVs), in contrast, are characterized by multiple concentric phospholipid bilayers separated by aqueous compartments. Their size typically ranges from tens of nanometers to several micrometers depending on the preparation method employed.[19,26,27]

Liposomes are primarily composed of phospholipid molecules, with commonly used phospholipids, including soy lecithin, egg lecithin, marine phospholipids, and milk phospholipids.[28,29] The addition of cholesterol regulates the fluidity of the phospholipid bilayer membrane, reduces membrane permeability, protects phospholipids from oxidation, and promotes lipid chain accumulation and bilayer formation.[30,31] The preparation methods encompass traditional approaches, such as thin-film hydration, solvent injection, multiple emulsions, reverse phase evaporation, gradient methods, and freeze-drying, as well as advanced technologies, such as supercritical fluid technology and microfluidic technology. Although numerous liposome preparation strategies have been described, each method has advantages and disadvantages (Table 1). Consequently, careful selection and judicious integration of these methods, tailored to the specific application context, are essential to maximize efficiency and achieve optimal outcomes.

2.1.1 Thin-film hydration method. The thin-film hydration method is widely employed in laboratory settings for liposome preparation owing to its operational simplicity.[32,33] In this process, phospholipids, cholesterol, other lipid components, and the target drug are initially dissolved in an organic solvent system, typically comprising chloroform, methanol, and/or ethyl ether. Subsequently, a homogeneous lipid film is formed on the inner surface of a rotary evaporation flask through solvent removal under reduced pressure. Upon the addition of the aqueous-phase medium and subsequent rotation under controlled conditions, the lipid film undergoes hydration, resulting in liposome formation. Although this method offers procedural simplicity, it is characterized by certain limitations, including heterogeneous particle size distribution and relatively low drug encapsulation efficiency.

In addition, the type of organic solvent, the type and proportion of surfactant, the cholesterol content, the time, and the temperature of mixing affect the properties of liposomes.[34] For instance, the physical characteristics of liposomes demonstrate substantial dependence on the solvent system employed. Specifically, the utilization of a chloroform-ether binary solvent system tends to produce LUVs, while the application of pure chloroform often results in smaller multilamellar vesicles.[35]

Mirveis *et al.*[36] developed a liposomal formulation by dissolving soybean phosphatidylcholine, cholesterol, and DSPE–PEG2000 in chloroform at a molar ratio of 2 : 1 : 0.16. The organic solvent was completely evaporated at 45 °C and 120 rpm to form a homogeneous lipid film. Subsequently, the film was hydrated with arsenic trioxide-containing PBS for 20 minutes, followed by ultrasonication, 10 freeze–thaw cycles, and centrifugation. The resulting liposomes exhibited an encapsulation efficiency of 77.3 ± 5.7%, a particle size of 108.0 nm, and a zeta potential of −2.95 mV. These liposomes were further functionalized by mixing with an anti-nucleolin aptamer solution, where the aptamer was immobilized on the liposome surface through either physical adsorption or chemical coupling. This functionalization imparted liposomes with the ability to target nucleolin-overexpressing cancer cells. Moreover, the cytotoxicity of the aptamer-conjugated liposomes on the HT-29 cancer cell line was significantly reduced compared to the arsenic trioxide treatment alone.

2.1.2 Solvent injection method. Solvent injection techniques include ether and ethanol injection methods.[37] When similar operational principles are shared, these methods are distinguished by the choice of organic solvent. In the ether injection approach, phospholipids, cholesterol, and the target

Table 1 Advantages and disadvantages of liposome preparation methods

Methods	Advantages	Disadvantages
Thin-film hydration method	Simple, laboratory-scale; high EE for lipophilic drugs (EE ≈ 60–80%)	Forms MLVs (1–5 μm); low EE for hydrophilic drugs; requires post-homogenization
Solvent injection method	One-step; yields SUVs (<100 nm); ethanol or ether injectable	Dilution risk; residual organic solvent; limited lipid solubility in ethanol
Multiple emulsion method	High EE for hydrophilic drugs; scalable	Multi-step; residual solvent; broad size distribution
Reverse-phase evaporation	High EE for hydrophilic drugs; suitable for LUVs (100–1000 nm)	Residual solvent; protein/peptide inactivation risk; complex protocol
Gradient method	Active drug loading and high encapsulation rate	Sensitive to lipid type/size; requires precise pH/ion gradient
Freeze-drying method	Sterile, pyrogen-free product; long-term stable	Requires cryo-/lyo-protectants; high cost; multi-step process
Supercritical fluidics technology	Solvent-free; tunable size (100–150 nm); scalable	High equipment cost; critical parameter control (P, T)
Microfluidic technology	Monodisperse liposomes (20–100 nm, PDI < 0.1); high throughput (>1 L h^{-1})	Channel clogging; high cost; requires flow-rate/temperature optimization

EE: encapsulation efficiency; MLVs: multilamellar vesicles; SUVs: small unilamellar vesicles; LUVs: large unilamellar vesicles; PDI: polydispersity index.

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drug are dissolved in the ether. The resulting organic phase is then gradually introduced into a preheated phosphate buffer (50–60 °C) under continuous magnetic stirring. The subsequent evaporation of ether facilitates the formation of drug-loaded liposomes.[38] The ethanol injection method employs ethanol as the solvent, where the organic phase is injected into the aqueous phase to form liposomes. Residual ethanol contributes to drug stabilization and encapsulation. Although this method is operationally simple and achieves a relatively high encapsulation rate, it suffers from limitations, such as a slow preparation speed and incomplete solvent removal. Consequently, it is primarily suitable for small-scale laboratory applications.[39,40]

Li *et al.*[41] prepared a homogeneous mixture of yolk phosphatidylcholine, cholesterol, DSPE–PEG2000, butyrate, and 4-octyl itaconate (4-OI) at a ratio of 100 : 25 : 60 : 50 : 10. The mixture was dissolved in ethanol to form a clear solution. This ethanolic solution was subsequently added dropwise into the PBS buffer under continuous magnetic stirring, resulting in 10% (v/v) ethanolic dispersion. The dispersion was then subjected to spinning and centrifugation at 12 000 rpm for 20 minutes, yielding liposomes with a mean particle size of 121.59 ± 0.29 nm and an encapsulation efficiency of 62.62 ± 2.49%. As a pivotal metabolite in the tricarboxylic acid cycle, 4-OI demonstrates significant therapeutic potential by inhibiting the release of high mobility group box 1 protein and suppressing the expression of Gasdermin E N-terminal fragment-mediated cytokines.[42] This compound specifically targets intestinal epithelial cells as an effective pyroptosis inhibitor, thereby preventing pyroptotic cell death in the intestinal epithelium. This protective mechanism facilitates mucosal repair in patients with ulcerative colitis, effectively reducing intestinal inflammation and promoting tissue integrity restoration.[41]

2.1.3 Multiple emulsion method. The multiple emulsion method is fundamentally based on the formation of a multilayered emulsion system achieved by dispersing the primary emulsion (commonly referred to as colostrum) in a distinct continuous phase. These systems are characterized as highly dispersed, as well as multi-phase structures with heterogeneous particle size distributions. Among the various types of multiple emulsions, water-in-oil-in-water (W/O/W) and oil-in-water-in-oil configurations represent the two most prevalent and widely studied forms.[43,44]

The preparation process involves dissolving phospholipids and cholesterol in organic solvents, followed by their incorporation into the drug solution intended for encapsulation. This mixture is then emulsified to form a primary oil-in-water (O/W) emulsion. Subsequently, the primary emulsion is dispersed into a large volume of aqueous phase to create a W/O/W multiple emulsion system. Liposomes are ultimately obtained through organic solvent removal under controlled temperature conditions. This well-established technology has been successfully implemented in the production of marketed pharmaceutical products and demonstrates excellent scalability for industrial manufacturing.[45] Notably, liposomal cytarabine exemplifies the therapeutic advantages of this technology. As an effective treatment for lymphomatous meningitis, this formulation demonstrates enhanced therapeutic efficacy compared to conventional preparations. Through targeted modification, it reduces drug metabolism and degradation while improving pharmacokinetic properties, ultimately leading to reduced cytotoxicity and improved clinical outcomes.[46]

2.1.4 Reverse-phase evaporation. The reverse-phase evaporation technique is a widely utilized method for liposome preparation. In this process, lipids are initially dissolved in an organic solvent, which is subsequently brought into contact with an aqueous phase containing the target substance for encapsulation. The system's phase behavior varies depending on the organic solvent's miscibility with water: it forms a single-phase system when using water-miscible solvents (*e.g.*, ethanol) or a two-phase system when employing water-immiscible solvents (*e.g.*, diethyl ether). In single-phase systems, phospholipid molecules disperse uniformly in the aqueous medium, while in biphasic systems, these molecules spontaneously arrange into a monolayer at the organic-aqueous interface.[47] The liposome formation process involves several sequential steps: first, water-in-oil (W/O) microemulsions are generated through ultrasonic treatment; second, organic solvents are eliminated using a rotary evaporator; and finally, phospholipid molecules reorganize into vesicular structures in aqueous medium. The resulting suspension is then passed through a polycarbonate filter membrane, yielding uniform monolamellar liposomes with controlled size distribution.[48]

Liu *et al.*[49] utilized this approach to synthesize liposomes (nano-Pt/VP@MLipo) with a diameter of approximately 140 nm, a zeta potential of −16.7 mV, an encapsulation efficiency of 48.2%, and a drug loading capacity of 15% for platinum nanoparticles. By integrating mouse macrophage membranes into the liposomal structure, they conferred biomimetic and targeting capabilities, which significantly reduced the inherent toxicity of nano-Pt. Furthermore, these engineered liposomes were designed to serve as catalytic oxygen suppliers, enhancing the efficacy of tumor photodynamic therapy. This innovative strategy resulted in substantial inhibition of invasive 4T1 tumor growth and pulmonary metastasis while significantly prolonging the survival of the treated animals.

This versatile method is universally applicable to various lipids, lipid mixtures, and small molecules, demonstrating exceptional capabilities in encapsulating genes, organic solvent-resistant drugs, and water-soluble compounds. However, a notable limitation lies in the temperature requirements during the preparation process, particularly during ultrasonication and organic solvent evaporation under reduced pressure, which may potentially denature heat-sensitive substances.[50]

2.1.5 Gradient method. The gradient method leverages the concentration or chemical nature differential between the interior and exterior of liposomes to facilitate drug encapsulation. Notably, this approach encompasses three established techniques: the pH gradient method,[51] acetate gradient method[52] and ammonium sulfate gradient method.[53] Among these, the pH gradient method involves preparing an internal buffer solution containing specific acidic components (*e.g.*, citrate and tartaric

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acid), followed by adjusting the external pH of liposomes using techniques such as dialysis or column chromatography to approximate physiological pH, thereby establishing a pH gradient across the liposomal membrane.[54] Under controlled temperature conditions, the target drug is mixed with pre-formed blank liposomes possessing the established gradient. In this system, the drug exists in a lipophilic neutral form in an external neutral pH environment, enabling its passive diffusion across the lipid bilayer. Once inside the liposome aqueous phase, the drug undergoes protonation, converting to an ionic form that is effectively trapped within the liposomal core. This innovative process achieves efficient drug encapsulation. Furthermore, both the ammonium sulfate gradient method and the calcium acetate gradient method operate on analogous principles for liposome preparation.

Hwang *et al.*[55] demonstrated that the encapsulation efficiency of liposomal diclofenac approached 100% when employing a calcium acetate gradient, while the pH gradient method yielded a 5–50% encapsulation efficiency for FITC-insulin liposomes. This suggests that weakly acidic drugs can be effectively loaded into liposomes *via* an acetate gradient, while the pH gradient method is particularly suitable for liposomal peptide preparation.

The nucleotide analogue dimeric aminobenzimidazole, a STING agonist,[56] faces the challenges of low serum stability and poor cell membrane permeability. To address these issues, Zhang *et al.*[57] successfully encapsulated dimeric aminobenzimidazole in liposomes using the ammonium sulfate gradient method, achieving a particle size below 150 nm. This reduced particle size minimizes rapid clearance by the reticuloendothelial system, thereby extending its circulatory time in the bloodstream. Furthermore, the lower surface charge of these liposomes decreases nonspecific binding to plasma proteins, enhancing both circulation duration and cellular permeability.

2.1.6 Freeze-drying method. The freeze-drying method is utilized to produce heat-free and stable sub-micron liposomes.[58] In this process, lipids and water-soluble additives are initially incorporated into W/O emulsions, followed by freeze-drying. For instance, lipids and water-soluble carrier materials (*e.g.*, sucrose) are dissolved in a tertiary butyl alcohol/water co-solvent system to form isotropic monolayers of liposomes. These are then filtered and sterilized using a sterile filter head, after which they are collected in freeze-drying containers. The resulting lyophilized product is subsequently rehydrated in an aqueous solution to generate a homogeneous suspension of liposomes.[59] Notably, the freeze-drying method enables drug loading at lower temperatures, significantly enhancing the storage stability of temperature-sensitive compounds, such as proteins, peptides, antibiotics, and vaccines.[60]

Tanaka *et al.*[61] employed this method to prepare mRNA–lipid nanoparticles by encapsulating *in vitro* transcribed messenger RNA (IVT-mRNA) into LNPs, thereby advancing mRNA-based therapeutic research. This approach addresses the challenges associated with IVT-mRNA because it is susceptible to enzymatic degradation in extracellular fluids and its hydrophilic nature hinders efficient cell membrane penetration.[62] To overcome these limitations, the researchers developed a "post-encapsulation" technique that involves mixing the IVT-mRNA solution with lyophilized empty LNPs, followed by brief heating. This strategy mitigates the inherent shortcomings of IVT-mRNA and significantly extends its storage stability.

2.1.7 Supercritical fluidics technology. Supercritical fluidics (SCFs) have garnered significant attention as environmentally friendly alternatives in the development of drug delivery systems. A schematic representation of the SCFs is illustrated in Fig. 2A. SCFs exhibit unique physicochemical properties that combine the characteristics of both liquids and gases, including high density and gas-like low viscosity, which facilitates superior mass transfer efficiency.[63,64] Among various SCFs, carbon dioxide has emerged as the most extensively utilized supercritical fluid owing to its cost-effectiveness, non-toxic nature, and relatively low critical pressure and temperature. The application of supercritical carbon dioxide as a non-toxic medium presents a viable alternative to conventional organic solvents in various pharmaceutical applications, particularly in drug particle engineering and nano-encapsulation technologies. These technologies include the supercritical anti-solvent process and the gas anti-solvent method.[65]

Irinotecan, a semi-synthetic derivative of camptothecin, is primarily employed in the treatment of colorectal cancer and small cell lung cancer. However, its clinical utility is significantly limited by its extremely short half-life, necessitating continuous intravenous infusion to maintain therapeutic efficacy, which may lead to cumulative toxicity.[66] To address this limitation, Mohammadi *et al.*[67] developed polyethylene glycol (PEG)-modified liposomes encapsulating irinotecan hydrochloride using supercritical fluid technology. The hydrophilic and flexible properties of PEG chains effectively prevent phagocytic uptake. Moreover, PEG forms a polymer layer on the liposome surface, which enhances surface hydrophilicity and induces mutual repulsion between the polymer coating and blood components. This shielding of surface charge prolongs the circulation time of liposomes in the bloodstream and indirectly extends the half-life of irinotecan hydrochloride. Compared to traditional methods, liposomes prepared using SCF technology exhibit smaller sizes and higher encapsulation efficiencies while eliminating the need for hazardous solvents. This technology is not only easy to operate but also highly suitable for large-scale industrial applications and can be readily adapted to industrial GMP processes.[67,68]

2.1.8 Microfluidic technology. Microfluidic chips represent innovative instrumentation platforms widely used in synthetic chemistry and biology, commonly referred to as microfluidic reaction systems. This technology enables material synthesis by precisely controlling the flow of minute liquid volumes through micron-sized channels. By utilizing microfluidic devices, high pressures are converted into intense shear forces, facilitating the preparation of liposomes without the need for ultrasound or toxic chemicals.[59,69] Furthermore, this technology offers precise control over reaction conditions. When the Reynolds number within the microchannel is significantly below 1, the fluid flow is predominantly laminar, with inertial forces dominating. Under such conditions, fluid mixing primarily relies on the passive diffusion of molecules, resulting in the rapid and efficient transfer of materials and heat. However, surfactants are often

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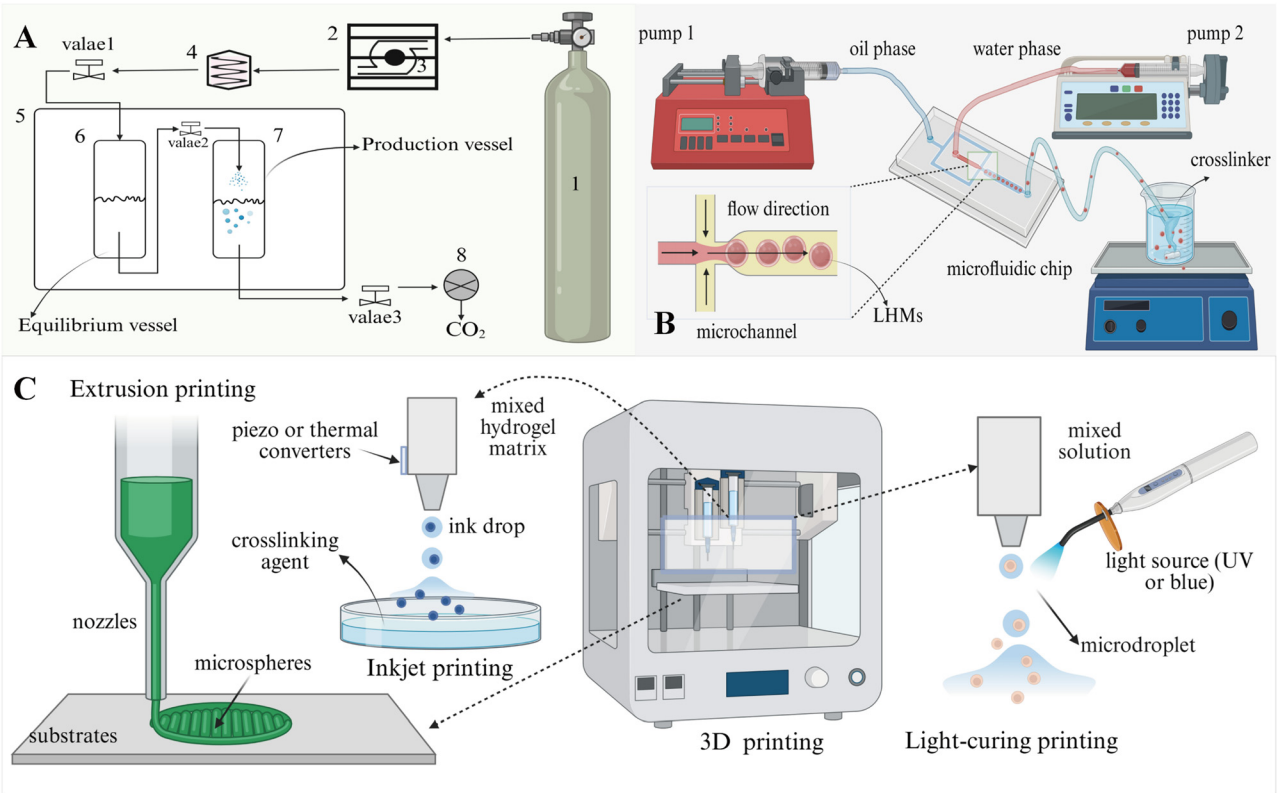

Fig. 2 Construction of liposomes and LHMs. (A) Schematic of the expansion supercritical fluid into an aqueous solution set up. (B) Schematic of the hydrogel microsphere fabrication process using microfluidics technology. (C) Schematic illustrating the application of 3D printing technology in preparing drug delivery systems for LHMs. Created using Biorender.com.

required to ensure smooth fluid flow and maintain stability, which may increase the risk of product contamination.[70]

Gu *et al.*[71] successfully synthesized baicalin-loaded liposomes using a microfluidic technique, achieving an exceptional encapsulation efficiency of 95.323 ± 0.481% and a uniform particle size distribution of 62.32 ± 0.42 nm. Compared to the free baicalin monomer, the fluorescence intensity of BCL-LPs in the zebrafish liver region gradually decreased as the concentration of baicalin increased. This observation indicates a significant suppression in the expression of the proto-oncogene *krasv12*, further demonstrating the enhanced anti-tumor efficacy of baicalin-loaded liposomes in the zebrafish model.

2.2 Construction of LHMs drug delivery systems

Hydrogels are three-dimensional polymer networks characterized by their exceptionally high water content (typically exceeding 90%) and serve as multifunctional platforms. Through structural and functional design, hydrogels have been successfully employed in a wide range of biomedical applications.[72] However, when liposomes are utilized for drug loading, they encounter challenges such as limited drug-loading capacity, inadequate resistance to enzymatic degradation, and short storage stability.[73,74] These limitations can be effectively addressed by homogeneously dispersing liposomes within the prepolymer solution of a hydrogel. This approach not only enhances the drug-loading capacity, stability, and bioavailability of the drug *in vivo* but also imparts a degree of resistance to enzymatic degradation, reduces enzyme-induced damage, and enables dual-controlled release capabilities. Subsequently, the addition of a specific cross-linking agent under suitable conditions (*e.g.*, temperature, pH, and light) induces a reaction between the prepolymer and the cross-linking agent, leading to the rapid formation of a three-dimensional hydrogel network.[3,75,76] Although the integration of liposomes and hydrogels confers dual sustained-release properties on the drug, there remains room for improvement in the delivery mode.

With the continuous advancement of hydrogel microsphere preparation technologies, various LHMs have been developed to address various disease models. Compared to single liposomes, LHMs exhibit enhanced stability and drug delivery efficiency, significantly prolonging the duration of drug action. Their controlled and sustained drug release capability ensures prolonged therapeutic activity at the target site, thereby reducing the frequency of administration and improving patient compliance. As a tissue engineering scaffold, hydrogel not only promotes cell proliferation, differentiation, and migration but also exhibits excellent biocompatibility, thereby minimizing drug-induced damage to healthy tissues and improving treatment safety.[77–80]

The synthesis strategies of LHMs primarily encompass microfluidics, electrospraying, 3D printing, and the reversed-phase microemulsion method. Microfluidic technology enables high-precision preparation by generating uniform droplets, making it particularly suitable for constructing complex

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structures with targeted functionalities. Electroray technology utilizes high-voltage static electricity to atomize liquid into microspheres, which is advantageous for drug loading and sustained-release applications. 3D printing offers the capability for personalized manufacturing although it is associated with relatively high equipment costs. The reversed-phase microemulsion method involves the inversion of oil–water phases to form nanoscale vesicle cells, which exhibit excellent stability and controllability. Each of these methods presents distinct advantages and limitations. Therefore, in practical applications, the selection of an appropriate technical route should be based on specific requirements and objectives.

2.2.1 Microfluidics. Microfluidics is a cutting-edge technique that enables the precise manipulation of fluids within micron-sized channel systems. By accurately regulating flow rates, this method facilitates the generation of droplets with uniform particle sizes and excellent dispersion. Subsequently, these droplets can be cured or polymerized to form microspheres using techniques such as ultraviolet (UV) curing or the addition of cross-linking agents.[75,81,82] A schematic diagram illustrating the preparation of microspheres using microfluidics is presented in Fig. 2B. This approach offers precise control over the particle size, shape, and surface properties of the microspheres, ensuring a highly controllable and reproducible preparation process. Consequently, microfluidics is particularly suitable for fabricating LHMs (liquid-core microcapsules) with complex structures (*e.g.*, core–shell configurations) and diverse functionalities.[83,84]

Li *et al.*[76] engineered liposomes by incorporating chondrogenic affinity peptides that specifically target chondrocytes, thereby endowing the liposomes with active chondrocyte-targeting capabilities. In their subsequent experiments, the researchers developed LHMs through a multi-step process: first, the modified liposomes were combined with methacrylated hyaluronic acid; second, oil-in-water droplets were generated using microfluidics; and finally, the droplets were cross-linked and cured under UV light. As depicted in Fig. 3, this methodology outlines the construction of the LHM's drug delivery systems. In this framework, methacrylated hyaluronic acid serves as a drug reservoir, leveraging its porous structure to not only enhance the loading capacity of the mitochondrial autophagy activator, urocortin A, but also to facilitate controlled drug release.

2.2.2 Electrospraying. Electrospraying is an advanced technique utilizing electrostatic forces to fabricate nanoparticles.[85,86] In this process, a drug-polymer solution is ejected through a magnetically charged nozzle into a collector. As the solution reaches the collector, the solvent evaporates, leaving the dry nanoparticles behind. The underlying mechanism can be summarized in three key steps: first, the drug-polymer solution is introduced through a charged nozzle; second, an electric field is established by applying a voltage between the nozzle and the collector; and third, under the influence of the electric field, the solution is atomized into fine droplets, which solidify into dry nanoparticles (typically <200 nm in size) upon solvent evaporation during their trajectory toward the collector.[87]

The characteristics of the resulting nanoparticles, including size and morphology, are influenced by various electrospray parameters, such as applied voltage, flow rate, nozzle-to-collector distance, solvent type, and the properties of the polymer solution (*e.g.*, type, viscosity, and electrical conductivity). By optimizing these parameters, particularly voltage and flow rate, researchers can precisely control microsphere particle size and encapsulation efficiency. However, despite its advantages, electrospraying presents several limitations, including high equipment costs, operational complexity, stringent material requirements, low production yield due to its slow preparation process, and safety concerns arising from the use of highly volatile solvents, which may also contribute to environmental contamination.[88]

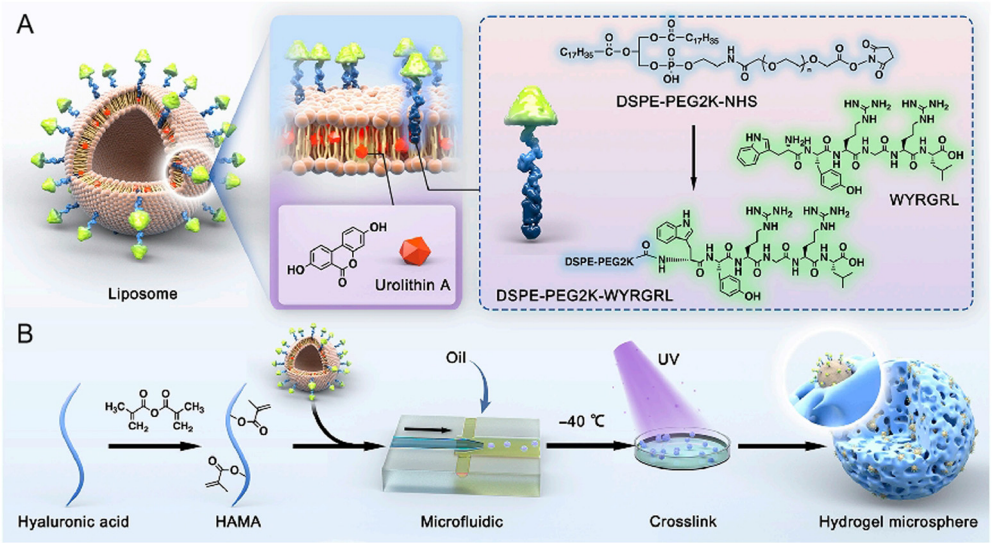

Fig. 3 Construction of mitochondria dynamically oriented hydrogel microspheres. (A) Liposomes loaded with UA and modified by WY (WY-Lip/UA). (B) Application of microfluidics to construct drug-loaded liposome composite hydrogel microspheres (HM@WY-Lip/UA). UA, urocortin A; WY, WYRGRL.[76] Copyright 2024. Reproduced with permission from Science and Technology Review Publishing House.

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Strasdat *et al.*[89] developed fluorescent drug-loaded microspheres using two distinct techniques: the electrostatic dropping method and the electrospray method. These methodologies were employed to investigate the release characteristics of lipophilic drugs within hydrogel microspheres. In the electrostatic dropping approach, fluorescent drug-encapsulated liposomes were combined with a 1% sodium alginate solution. The mixture was subsequently crosslinked and solidified by introducing it dropwise into a continuously stirred $CaCl_2$ solution. This process was conducted under a constant 5 kV electrostatic potential for 30 minutes. Conversely, the electrospray method involved atomizing the mixture directly into the $CaCl_2$ solution to form microspheres. The experimental results demonstrated significant variability in drug transfer rates, with larger microspheres (~330–1360 μm) exhibiting prolonged transfer durations (24–57 minutes), while smaller beads (<50 μm) showed accelerated transfer kinetics (~1.4 minutes).

2.2.3 3D printing. The primary methods for 3D printing LHMs encompass light-curing techniques (*e.g.*, Stereo Lithography Apparatus and Digital Light Processing), inkjet printing, and extrusion-based approaches (*e.g.*, Direct Ink Writing and Fused Deposition Modeling). Light-curing printing[90,91] offers superior resolution, typically achieving micron-scale precision, and enables the fabrication of complex geometrical structures. Nevertheless, this technique is constrained by several factors: the uniformity of the light source affecting print accuracy, limited resolution capabilities, elevated equipment costs that hinder large-scale production, and the necessity for specialized operational expertise. Huang *et al.*[92] utilized digital light processing technology, a light-curing 3D printing method, to develop a digital light processing printing platform based on a full peptide hydrogel. By optimizing critical parameters, such as blue light exposure time and layer thickness, they achieved the fabrication of complex structures, including hexagonal petals, microporous scaffolds, and ear models. The printing process exhibited a resolution of 0.5 mm and an error of 0.122 mm, demonstrating high efficiency and accuracy in 3D structure fabrication.

Inkjet printing[93] demonstrates high resolution and flexibility, making it particularly suitable for fabricating intricate two- or three-dimensional structures. However, material viscosity constraints can lead to nozzle clogging issues, necessitating frequent maintenance and cleaning procedures. Extrusion printing,[94] while being a well-established technology with comparatively lower equipment costs, exhibits reduced molding accuracy relative to light-curing techniques, typically operating at speeds in the range of 0.1–0.2 mm s^{-1}. Notably, this method enables the fabrication of LHMs with sophisticated internal structures and functional complexities (Fig. 2C).

The 3D printing of LHMs represents an advanced fabrication technology that involves multiple critical steps. Initially, a hydrogel precursor solution incorporating liposomes must be prepared, typically comprising hydrogel materials, liposomes, and various biologically active components. This hybrid solution is subsequently subjected to layer-by-layer deposition using 3D printing technology, where precise control is maintained under specific environmental conditions, including temperature regulation, light intensity, and chemical crosslinking agents, to achieve the desired geometric configurations and structural features. The principal advantages of this technology include precise modulation of drug or bioactive molecule release kinetics and spatial distribution while preserving their biological efficacy. Furthermore, 3D printing facilitates personalized medicine through the customization of implants or dressings tailored to specific anatomical shapes and functional requirements.[95,96]

Eugster *et al.*[97] employed 3D printing technology to fabricate injectable LHMs designed for the localized treatment of abdominal peritoneal diseases, including peritoneal carcinomatosis, postoperative adhesions, and peritoneal fibrosis. Furthermore, the study developed a sustained-release 3D-printed composite system incorporating the tyrosine kinase inhibitor gefitinib. This innovative approach aimed to address the pharmacokinetic challenges associated with gefitinib, such as its rapid systemic clearance and limitations in intraperitoneal administration, thereby enhancing its therapeutic efficacy.

2.2.4 Reverse microemulsion method. The reverse microemulsion method involves inverting the aqueous and oil phases, rendering the aqueous phase continuous while dispersing the oil phase.[98] The resulting microemulsions are encapsulated with surfactants, forming nanoscale vesicular pools. The dispersion of these vesicles in the oil phase indicates the formation of O/W microemulsions. Microemulsions typically consist of four components: a surfactant, a co-surfactant, an aqueous phase and an oil phase. They have a smaller particle size and larger specific surface area, as well as superior stability, controllability and tunability.[99,100]

Wang *et al.*[101] utilized this method to fabricate LHMs incorporating haemagglutinating factors, offering an alternative to traditional dressings by promoting rapid hemostasis and enhancing wound healing. In their study, sodium alginate and silk peptide served as the aqueous phase, while Ca^{2+} was employed as the cross-linking agent. By modulating the silk peptide concentration, the microspheres exhibited a remarkable water absorption rate of 1050% and a pore size of 19.59 nm.

2.2.5 Physical adsorption. The physical adsorption method, as the name implies, involves the adsorption of drug-loaded liposomes onto hydrogel microspheres. Although this method is straightforward and easy to implement, its drug release kinetics and resistance to enzymatic degradation remain inferior compared to microspheres fabricated through homogeneous mixing. In a related study, Han *et al.*[102] developed a 3D-printed porous bioceramic scaffold (β-TCP) inspired by the "lotus seedpod" structure, which was integrated with liposomal hydrogel microspheres loaded with desferrioxamine (DFO) to accelerate bone defect repair. GelMA microspheres and DFO liposomes were prepared using the microfluidic technique and the inverse evaporation heating method, respectively. Subsequently, DFO liposomes were adsorbed onto GelMA microspheres to form GML composite microspheres, which were then injected into β-TCP scaffolds. Follow-up studies revealed that this composite scaffold enhanced the osteogenic differentiation of bone marrow

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mesenchymal stem cells (BMSCs) and exhibited significant angiogenic potential.

In summary, each fabrication strategy exhibits distinct merits and constraints. Microfluidic and electrospraying techniques enable the reproducible preparation of monodisperse microspheres with sub-micron precision; however, their elevated equipment costs and limited scalability impede routine large-scale production. 3D printing technology can achieve personalized manufacturing of complex structures, but the equipment and technical threshold are high. The reverse phase microemulsion method has good controllability and stability, but the process is complicated and may involve organic solvents. Finally, the physical adsorption method is simple to operate, but its performance is relatively poor.

3. Performance optimisation of LHMs drug delivery systems

3.1 Selection of materials, concentrations and preparation conditions on LHMs

The selection of constituent materials, optimization of concentrations, and manipulation of preparation conditions are pivotal factors that markedly influence the drug-loading efficiency of LHMs delivery systems. Among these parameters, the judicious selection of phospholipid species plays a decisive role in determining liposomal stability, membrane fluidity, and permeability characteristics. Furthermore, precise adjustment of membrane material concentration and strategic modifications significantly impact the physical properties of lipid membranes, consequently affecting the particle size distribution and colloidal stability of liposomes.[29] Regarding the hydrogel matrix in LHMs drug delivery systems, the choice of synthetic material exerts profound effects on both drug release kinetics and biocompatibility profiles. Therefore, a comprehensive evaluation of material properties, including encompassing biosafety, water absorption capacity, chemical stability, physical resilience, and biocompatibility, is imperative during the selection process.[103,104]

3.1.1 Factors affecting liposome synthesis. The phospholipids used in synthetic liposomes fall into two main categories: natural phospholipids and synthetic phospholipids. Natural phospholipids are mainly represented by lecithin (phosphatidylcholine (PC)), which is primarily derived from egg yolk and soya beans and is neutral; synthetic phospholipids mainly include DPPC (dipalmitoylphosphatidylcholine), DPPE (dipalmitoylphosphatidylethanolamine), and DSPC (distearylphosphatidylcholine), which are famous for their strong stability, high antioxidant property, and good stability of finished products.[105]

Cholesterols and phospholipids constitute the fundamental structural components of liposomes and play a pivotal role in modulating membrane fluidity, thus serving as a "fluidity buffer" for the liposomal system. Notably, various wall materials exhibit distinct effects on liposomal encapsulation efficiency.[31] For instance, Gładkowski *et al.*[106] demonstrated that liposomes incorporating soy sterols exhibited markedly enhanced rigidity and elevated phase transition temperatures in their hydrophobic regions compared to cholesterol-containing formulations. However, excessive cholesterol proportions may compromise liposome integrity. Elevated cholesterol content reduces phospholipid concentration, leading to impaired membrane formation, reduced structural stability, and increased susceptibility to membrane damage. Comparative studies using phytosterols, which are structurally analogous to cholesterol (*e.g.*, leguminous stanols, β-sitosterol), revealed superior encapsulation efficiency in identical formulations compared to cholesterol-based systems.[107]

Furthermore, the incorporation of auxiliary wall materials, specifically Tween 80, resulted in a notable reduction in particle size as the concentration of Tween 80 increased. This reduction was accompanied by a significant enhancement in the embedding efficiency of liposomes.[108] Additionally, the surface modification of liposomes using hydrophilic polymers, such as PEG, has been demonstrated to extend the retention time of liposomes in the circulatory system. This modification also minimizes the recognition and subsequent clearance of liposomes by the mononuclear phagocyte system.[109,110] Moreover, the composition and concentration of the hydrogel microsphere matrix play a crucial role in influencing both the drug release rate and the biocompatibility of the system.

3.1.2 Factors affecting hydrogel synthesis in LHMs. The selection of different hydrogel matrices (*e.g.*, chitosan, gelatin, alginate, and GelMA) and application of different concentrations affect the degree of cross-linking, swelling, and biodegradability of the hydrogel, which in turn influence the drug release characteristics.[111] Specifically, the concentration of the hydrogel matrix determines both the cross-linking density and mechanical strength of the hydrogel. A high concentration may result in excessive density, impairing drug release and cell permeation. Conversely, a low concentration may lead to insufficient mechanical strength, compromising the effective immobilization of liposomes.[3]

Preparation conditions, such as temperature, pH, and cross-linking agents, play a critical role in determining the structure and properties of liposome composite hydrogel microspheres. For instance, temperature directly influences both the stability of liposomes and the cross-linking degree of hydrogels during preparation. Variations in pH can alter the charge state and stability of liposomes, as well as the solubility and degradation behavior of hydrogels.[17] Furthermore, by adjusting the type or concentration of hydrogel cross-linking agents, the cross-linking density of hydrogel microspheres can be optimized. This optimization not only enhances their mechanical strength and water absorption properties but also increases drug loading capacity to a certain extent.[112]

Both liposome and hydrogel microsphere surfaces can be functionalized with specific antigens, antibodies, or ligands to achieve active or passive-targeted drug delivery.[113] Such targeted modifications facilitate precise drug delivery, minimize toxic side effects, and enhance therapeutic efficiency.[114] Depending on their solubility, drugs can be categorized as either water-soluble or fat-soluble. Water-soluble drugs are encapsulated within the aqueous core of liposomes, while fat-soluble drugs

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Table 2 Drug delivery system for LHMs

			Liposome			Hydrogel					
Number	Christen	Method	Structure	Size (nm)	Payload	Structure	Size (μm)	Function	Study type	Applications	Ref.
1	ChsMA@Lipo	Electrospraying	HSPC, mPEG2000-DSPE, cholesterol	122.3 ± 56.5	Liquiritin	ChsMA, Chs, sodium alginate	220 ± 61	Controlled-release	*In vitro* (chondrocytes)	Osteoarthritis	22
2	MELs	Reverse-phase evaporation	PC, cholesterol, DPPC	50–800	HBsAg	Poly(L-lysine), alginate	400.00	Controlled-release, protection	*In vivo* (HBsAg immunised mice)	Vaccine delivery	78
3	PPD-Lipo@HMs	Microfluidics	HSPC, egg yolk lecithin	118.50 ± 2.24	20(S)-protopanaxadiol (PPD)	Chinese herbal *Bletilla striata* polysaccharide	332.35 ± 22.24	Controlled-release, Microenvironment response	*In vitro* (RAW264.7)	Diabetic wound tissue repair	83
4	RAPA@Lipo@HMs	Microfluidics	HSPC, cholesterol, octadecylamine	102.3 ± 35.2	Rapamycin (RAPA)	Methacrylated hyaluronic acid	—	Controlled-release, protection	*In vitro* (C-28/I2 cells)	Osteoarthritis	116
5	GEF-loaded liposome gel beads	3D printing	S80, DPPC	—	Gefitinib (GEF)	Sodium alginate	S80: 686 ± 49 DPPC: 712 ± 43	Controlled-release, biological adaptation	*In vitro* (Huh-7 cells)	Intraperitoneal (IP) administration	97
6	GM@PDA@Lipo-Ebselen	Microfluidics	Cholesterol, lecithin	141.00 ± 20	Ebselen	Gelatin, methacrylic anhydride, polydopamine	GelMA-microspheres: 96 ± 7	Controlled-release, adhesion	*In vivo* (outer hair cells)	Treatment of hearing impairment	117
							PDA-grafted: 97 ± 8		*In vitro* (HEI-OC1 cells)		
7	ChSMA-RGD microspheres	Microfluidics	HSPC, DOPE, cholesterol, octadecylamine	177.74 ± 11.95	TGF-β1	ChsMA, LAP, EFL	117.85 ± 24.16	Physical lubrication, mechanical protection	*In vitro* (BMSCs, M1)	Osteoarthritis	118
8	Cur-R-CCMBs	Coacervation/extrusion/precipitation	Phospholipids, rhamnolipids	116.00 ± 70	Curcumin	Chitosan, κ-carrageenan	—	Controlled-release	*In vivo* (male BALB/c mice)	Chronic wound infections caused by drug-resistant pathogens	119
9	A-Lipo/PAHM	Microfluidics	Cholesterol, lecithin	102.3 ± 0.7	ABT263	Hyaluronic acid, methacrylic anhydride	200.6 ± 16.6	Targeted, Controlled-release, Promoting repair	*In vivo* (BMSCs, BMDMs)	Osteoarthritis	120
10	AST NSC/HSA-PEG Liposomes @SA/CMCS Microspheres	Physical cross-linking	Cholesterol, lecithin, NSC, HSA, AST	83.00	Astaxanthin (AST)	SA, CMCS	—	pH responsive, controlled release	*In vitro* (Caco-2 cells, HepG2 cells)	Hypercholesterolemia	121
11	E7-Lipo@Alg/Cs	Gas microfluidics	E7-peptide, ecithin, DSPE-PEG2K-NHS	152.98 ± 1.54	Fisetin	Alginate, chitosan	320 ± 11.0	Targeted, protection, controlled-release	*In vitro* (BMSCs)	Osteoporosis	122

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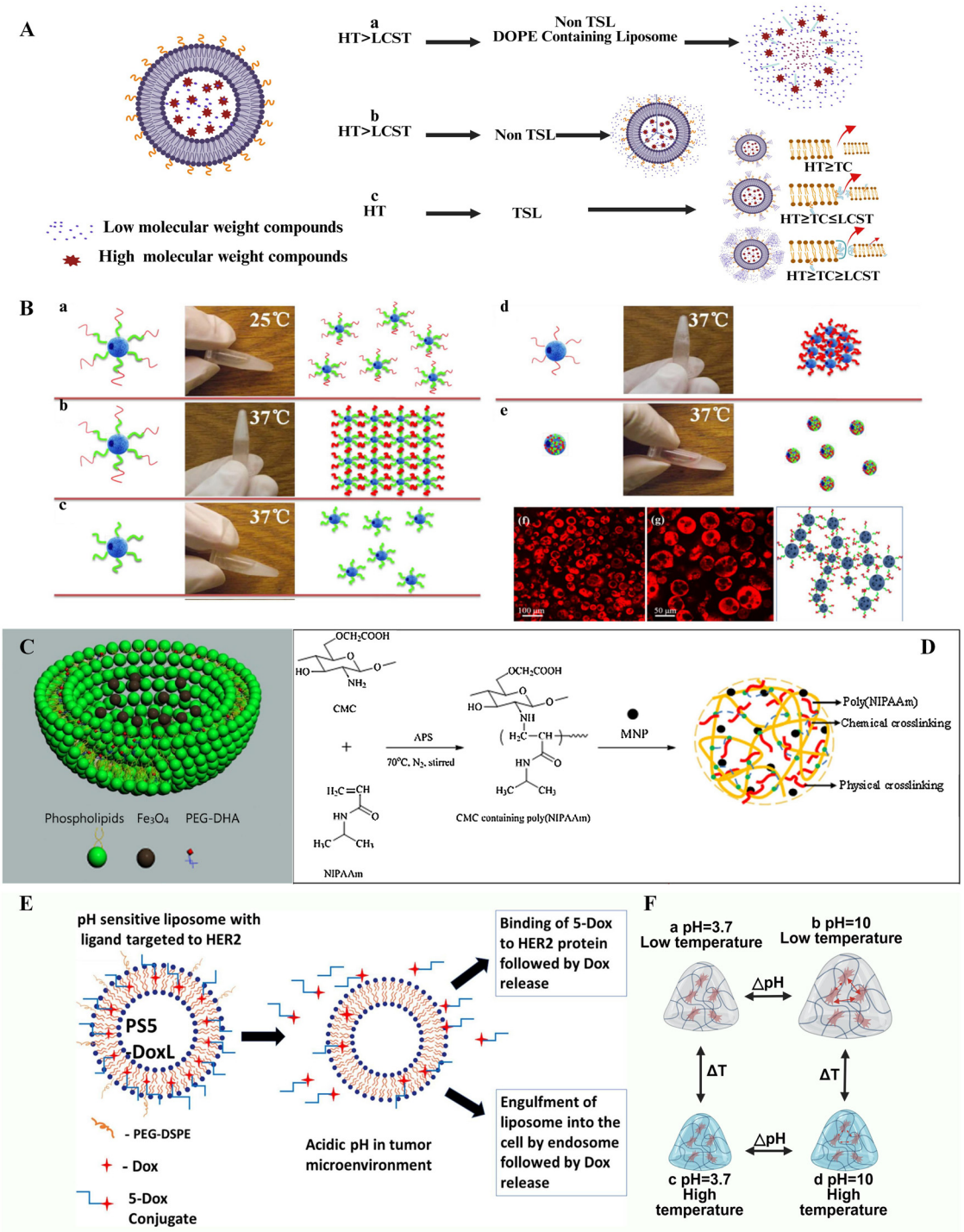

Fig. 4 Environmentally responsive modification of liposomes or hydrogels in LHMs. (A) Schematic of the mechanisms underlying heat-triggered content release from liposomes with distinct lipid compositions. In TSP-modified liposomes containing DOPE, the thermal behavior of TSP-modified liposomes is governed by the thermal activity of temperature-sensitive polymers (TSPs). The phase transition of TSP exerts structural pressure on the liposome membrane, inducing a transition from a bilayer to a hexagonal phase and ultimately leading to liposome disintegration. TSPs, temperature-sensitive polymers; TSLs, temperature-sensitive liposomes; Tc, transition temperature; LCST, lower critical solution temperature; HT, hyperthermia.[123] Reproduced with permission. Copyright 2022, Elsevier B.V. (B) Phase transition of temperature-sensitive hydrogels at room temperature and 37 °C.[124] Copyright 2020. Reproduced with permission from Wiley. (C) TEM image of the DHA-MLP NPs.[125] DHA, dihydroartemisinin. Copyright 2016. Reproduced with permission from Elsevier B.V. (D) Schematic for preparing a composite CMC microsphere containing poly(NIPAAm) and MNP. CMC, carboxymethyl chitosan; MNP, magnetite nanoparticle; APS, diammonium peroxodisulphate.[126] Copyright 2018. Reproduced with permission from Elsevier B.V. (E) Schematic representation of PS5-DoxL preparation and its targeting mechanism.[127] Copyright 2022. Reproduced with permission from Elsevier B.V. (F) Schematic representation of RC microsphere pH responsiveness. RC: rotameric cross-linker.[128] Copyright 2017. Reproduced with permission from Wiley.

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are embedded within the lipid bilayer or adsorbed onto the liposome surface.[115]

The preparation process of LHMs typically involves two sequential stages. Initially, drug-loaded liposomes are fabricated and subsequently modified to incorporate specific functionalities, including targeting capabilities and environmental responsiveness. In the subsequent stage, the prepared liposomes are integrated with a hydrogel matrix to form composite-structured microspheres. We have systematically reviewed and summarized recent advancements in the development of LHMs drug delivery systems, as comprehensively tabulated in Table 2.

3.2 Environmental response characteristics

To confer personalized environmental response properties to LHMs, the modification of either liposomes or hydrogel microspheres is imperative. Here, we delineate various modification techniques applied to these components, ensuring that the entire delivery system acquires specific environmentally responsive characteristics.

3.2.1 Temperature sensitive. Temperature-sensitive modification of liposomes is mainly achieved by both post-insertion and addition of temperature-sensitive polymers (TSP) to the organic phase, where the TSP is immobilised by the addition of lipid-soluble anchoring units for thermally triggered release of the drug at a specific temperature (Fig. 4A). Post-insertion method: the polymer is inserted into pre-formed liposomes; this method is convenient and fast but is limited to the outer surface of the liposome containing TSP, and this method allows the drug to enter the liposome by remote loading, but the presence of TSP may limit the remote loading of the drug as this usually requires heat. Addition of TSP to the Organic Phase: If TSP is soluble in the organic phase, it can be added to the lipid mixture, and this approach allows the polymer to modify both the inner and outer surfaces of the liposome, resulting in a sharper and more intense thermally triggered release at the polymer's lower critical solution temperature (LCST).[123]

Fu *et al.*[129] developed a temperature-sensitive liposomal nano-inducer, NIL-IM-Lip, which was modified with the photothermal agent IR 780 and loaded with the IDO 1 inhibitor 1-MT. This innovative system was designed to activate photothermal therapy, thereby inducing an immunogenic cell death effect. Simultaneously, the encapsulated 1-MT was utilized to modulate the tumour lymph node immune microenvironment by alleviating Treg inhibition and reversing the immunosuppressive environment. Additionally, 1-MT contributed to the activation of T cells and NK cells, promoting the remodelling of the tumour lymph node immune microenvironment. This dual-action approach significantly enhanced the efficacy of tumour immunotherapy by synergistically combining photothermal therapy and immune modulation.

Temperature-sensitive modification of hydrogels begins with the judicious selection of monomers and polymers.[130] Notably, pNiPAAm has emerged as one of the most extensively investigated temperature-sensitive systems, exhibiting an LCST at approximately 32 °C. To engineer hydrogels with the desired properties, hydrophilic or hydrophobic monomers are incorporated into the polymer matrix through chemical or physical cross-linking methodologies, thereby forming a three-dimensional cross-linked network. The modulation of the polymer's LCST allows for precise control over the hydrogel's hydrophilicity and responsiveness to thermal stimuli. In a seminal study conducted by Zhao *et al.*,[124] a biodegradable triblock copolymer, PLLA–PEG–PNIPAm, was meticulously designed and synthesized. This advanced polymer was subsequently employed to fabricate nanofiber-based temperature-responsive gel microspheres through self-assembly, specifically targeting cardiac regeneration. The unique property of this polymer lies in its ability to exhibit liquid-like characteristics at ambient temperature while rapidly transforming into a stable three-dimensional hydrogel matrix under physiological conditions. Post-transplantation, nanofiber-based temperature-responsive gel microspheres significantly enhanced cardiomyocyte survival and improved functional cardiac recovery (Fig. 4B).

3.2.2 Magnetic sensitivity. Magnetic materials with particle sizes ranging from 10 to 20 μm have been successfully integrated into liposomes using various methods, including physical encapsulation,[131] chemical coupling,[132] embedding[133] and co-precipitation.[134] These materials encompass monomers (*e.g.*, pure iron, cobalt, and nickel), alloys (*e.g.*, iron-nickel alloys and iron-aluminium alloys), oxides (*e.g.*, Fe_3O_4, FeO, Fe_2O_3, MO, and BaO), and hybrid magnetic materials. The incorporation of these magnetic components endows liposomes with targeting and localization capabilities under the influence of external magnetic fields.[18,131,134,135]

Li *et al.*[125] developed an innovative synthesis of magnetic dihydroartemisinin nanoliposomes (DHA-MLPs) through an optimized thin-film dispersion–sonication technique. This novel formulation ingeniously combines Fe_3O_4 nanoparticles with dihydroartemisinin (DHA), demonstrating remarkable anticancer efficacy (Fig. 4C). The synthesized DHA-MLPs exhibited an average particle size of 209.10 ± 4.92 nm, a zeta potential of −37.13 ± 1.01 mV, and a high drug encapsulation efficiency of 82.12 ± 0.91%. Additionally, the saturation magnetization strength (M_s) was measured to be 11.84 emu g^{-1} at room temperature. The study further revealed that the magnetized liposomes significantly enhanced the targeting ability, biocompatibility, and tumor inhibition effect of DHA compared to their non-magnetized counterparts.

Methods for preparing magnetic hydrogels:[18] (1) blending method: in this approach, magnetic nanoparticles are thoroughly mixed with the hydrogel precursor, followed by the initiation of the polymerization reaction. The uniform distribution of nanoparticles within the hydrogel matrix ensures consistent magnetic properties throughout the material. (2) Grafting method: this technique utilizes functionalized magnetic nanoparticles grafted with specific functional groups. These modified nanoparticles are co-polymerized with monomers, forming covalent bonds that integrate the magnetic particles into the hydrogel network. The covalent linkage enhances the stability and durability of the magnetic hydrogel. (3) *In situ* precipitation method: the hydrogel is first immersed

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in a concentrated solution containing the desired metal ions until swelling equilibrium is achieved. Subsequently, the hydrogel is treated with an alkaline solution, which induces the precipitation of magnetic nanoparticles within the hydrogel matrix. This method allows for precise control over nanoparticle size and distribution. (4) Swelling method: this method involves incubating the pre-formed hydrogel in a magnetic fluid. This is particularly suitable for the development of microgels because the swelling process facilitates the incorporation of magnetic nanoparticles into the hydrogel network. The simplicity and scalability of this method make it attractive for various biomedical applications.

Rodkate *et al.*[126] successfully synthesized hydrogel microspheres incorporating magnetite nanoparticles ($FeCl_3$ and $FeCl_2{\cdot}4H_2O$) using PNIPAM and CMC as the matrix. Synthesis was achieved through oil-in-water emulsion polymerization combined with cross-linking techniques, which were specifically designed to enable precise control over drug release (Fig. 4D). The experimental results demonstrated that the microspheres containing magnetite nanoparticles exhibited an M_s of 54.5 emu g^{-1}, which was approximately 15 times higher than that of microspheres without magnetic nanoparticles. Furthermore, it was revealed that the M_s value decreased with an increase in the content of organic components, highlighting the critical role of composition in determining the magnetic properties of the material.

3.2.3 pH-sensitivity. pH-sensitive modifications, whether applied to liposomes or hydrogels, are achieved by incorporating pH-responsive materials, thereby endowing these systems with specific pH-sensitivity. The principal methodologies for fabricating pH-sensitive liposomes can be categorized as follows:[136–138] (1) phospholipid-based systems, (2) polymer-anchored architectures, (3) *N*-isopropylacrylamide-based copolymer assemblies, (4) poly(ethylacrylic acid) formulations, (5) polyphosphoric acid ester constructs, (6) poly(ethylene glycol) derivative-based systems, and (7) poly(2-ethylpropylacrylic acid) compositions.

Sonju *et al.*[127] successfully developed pH-sensitive liposomes (PS 5-DoxL) encapsulating peptide mimetic-doxorubicin (5-Dox) with a particle size of 170.34 ± 3.75 nm, a zeta potential of −24.57 ± 4.68 mV, and a high drug encapsulation efficiency of 88.45 ± 1.50%. The drug release profile of PS 5-DoxL was evaluated under simulated physiological conditions at pH 6.5 and pH 7.4 for 6 hours (Fig. 4E). The study revealed that approximately 64% of 5-Dox was released under acidic conditions (pH 6.5), compared to only 48% under neutral conditions (pH 7.4). These findings indicate that the liposomes exhibit enhanced drug release efficiency in acidic environments, highlighting their potential for targeted drug delivery in pH-dependent applications.

The preparation of pH-responsive hydrogels typically involves the incorporation of pH-sensitive chemical bonds or structures, enabling the hydrogels to modulate their physical or chemical properties in response to varying pH environments. Primary preparation methods include[137] (1) the introduction of pH-sensitive chemical bonds, (2) the use of pH-sensitive monomers, and (3) the utilization of pH-sensitive polymers. For instance, Kureha *et al.*[128] developed cyclodextrin-crosslinked microspheres featuring decoupled thermal and pH-responsive volume transitions. These microgels control their swelling/shrinking behavior by regulating the aggregation/depolymerization state of γ-cyclodextrin within the RC network (Fig. 4F). Moreover, the aggregation and depolymerization of the RC network, and consequently the swelling capacity of the microgel, can be similarly modulated by adjusting the pH value.

3.2.4 Photosensitive liposomes. Photosensitive liposomes are meticulously engineered by incorporating photosensitive components that meet stringent criteria, including stability under physiological conditions, superior biocompatibility, and compatibility with liposomal structures. Several strategies have been developed to integrate these photosensitive components into liposomes, as outlined below:[139,140] (1) direct insertion: *i.e.*, during hydration of the lipid membrane, the photosensitive component is mixed with the lipid, thus forming liposomes. (2) Post-assembly: pre-formed liposomes are exposed to the photosensitive component, which is subsequently embedded into the liposomal membrane through diffusion or post-insertion techniques. (3) The photosensitive component is anchored to the outer membrane of the liposome *via* covalent bonding or non-covalent interactions, ensuring its immobilization on the liposomal surface. The mechanism of light-triggered release primarily involves photoisomerization and conformational changes in the photosensitive components, as well as photothermal effects that induce thermally triggered release. Furthermore, critical factors, such as light wavelength, intensity, and duration, must be carefully considered because they significantly influence the kinetics of the release process.

Enzian *et al.*[141] embedded four photosensitisers (BPD, Ce6, $AlPcS_2$ and 5,10-DiOH) in liposome membranes. Upon light excitation at a wavelength of 420 nm, these photosensitizers generated singlet oxygen species and other reactive oxygen species. This oxidative activity induced chain scission and lipolysis of the liposome membranes, thereby facilitating the release of the encapsulated drug. The results demonstrated that liposomes containing 5,10-DiOH achieved more than 80% fluorescein release within just 2 minutes under 420 nm light excitation. Notably, 5,10-DiOH exhibited significantly higher efficiency compared to the other three photosensitizers.

Photosensitive hydrogels are synthesized through the integration of photosensitive precursors and photoinitiators, facilitating cross-linking or depolymerization reactions between free radicals and functional groups under specific light conditions, such as UV or blue light irradiation.[142,143] Although these hydrogels can modulate material microstructure through precise control of spatial cross-linking or depolymerization, thereby influencing cell behaviors, including attachment, migration, and differentiation, it is noteworthy that UV irradiation may generate free radicals. These free radicals possess the potential to induce DNA damage and cellular dysfunction.[144]

Pourbadiei *et al.*[145] successfully synthesized a copolymer by integrating azobenzene derivatives with *N*-isopropylacrylamide, which served as a dual-responsive component to light and heat. They further developed a Paclitaxel-loaded DAS@SCD/NIPAZO hydrogel by establishing a host–guest interaction between β-cyclodextrin and azobenzene groups. This hydrogel exhibited

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a 34% higher drug release rate under 365 nm light irradiation compared to the control without light at the same temperature.

3.2.5 Immunoliposome. Immunoliposomes are engineered by conjugating antibodies to the liposome surface through two primary mechanisms: covalent and non-covalent coupling.[146,147] Covalent coupling typically involves the formation of a stable thioether bond, which is achieved through reactions, such as the conjugation of a thiol group with a maleimide moiety, which firmly anchors the antibody or other ligands to the liposome surface. In contrast, non-covalent coupling leverages interactions between a hydrophobic anchoring moiety and functional groups, facilitating ligand binding to the liposome surface to achieve active tissue targeting.

Rahman *et al.*[148] developed chimeric nanobodies (cNB) by isolating peripheral blood mononuclear cells from immunized alpacas to generate nanobodies targeting human epidermal growth factor receptor 2 (HER2). Subsequently, the cNB were combined with lipids at a specific ratio using ultrasonication and extrusion techniques to formulate immunoliposomes (cNB-LP) with a uniform particle size of 100 nm. These cNB-LPs demonstrated efficient drug-loading capacity and selective targeting of HER2-overexpressing cancer cells, exhibiting significant therapeutic efficacy in both *in vitro* and *in vivo* experiments.

After implementing the aforementioned optimization strategy, it is imperative to conduct a comprehensive validation of the delivery system. This validation process should encompass a thorough investigation of the system's drug-loading efficiency, release kinetics, biocompatibility, and pharmacodynamic characteristics through both *in vivo* and *in vitro* experiments. These evaluations are crucial to ensure that the delivery system satisfies the practical requirements for clinical applications. Furthermore, the delivery system should be systematically refined and enhanced based on experimental findings to optimize its performance. The modification strategies and related response materials are shown in Table 3.

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4. Biomedical applications

4.1 Cardiovascular disease

In the treatment of cardiovascular disease, there are several difficulties, including drug efficacy and tolerance, short drug half-lives, drug combinations that increase efficacy but increase the risk of adverse events, and difficulty in measuring drugs (peptides, such as angiotensin 1–7, angiotensin 1–9, or alamandine, are difficult to isolate from biological samples owing to the similarity in molecular structure), and studies have shown that high cholesterol is an important risk factor for cardiovascular disease.[149,150]

AST exhibits multiple therapeutic properties, including antioxidant, anti-proliferative, anti-apoptotic, and anti-inflammatory effects. However, its clinical application is limited by poor bioavailability, low solubility, and chemical instability.[151] To address these challenges, Liu *et al.*[121] developed an innovative drug delivery system utilizing AST NSC/HSA-PEG liposomes@SA/CMCS. This system overcomes AST's inherent limitations and demonstrates targeted delivery to intestinal epithelial cells through neonatal Fc receptor binding, enabling sustained release in the intestinal environment. Importantly, this formulation effectively prevents diet-induced hypercholesterolemia associated with a high-fat-high-cholesterol diet. Furthermore, the liposome composite hydrogel has shown therapeutic potential in cardiovascular applications by ameliorating mitochondrial dysfunction in myocardial infarction regions and promoting angiogenesis, thereby significantly improving myocardial function.[152]

4.2 Bone and cartilage diseases

The treatment of bone and cartilage diseases, particularly osteoarthritis, faces two critical challenges: maintaining long-term joint cavity lubrication and preserving the morphology of cells delivered to the joint space.[116,153,154] Conventional drug delivery approaches, including oral administration and intravenous injection, are often associated with suboptimal drug bioavailability and systemic adverse effects. In comparison, localized administration strategies, particularly intra-articular injection, alleviate these shortcomings; however, they require repeated administration owing to the rapid clearance of the delivery vehicle and premature release of therapeutic agents, which ultimately compromises therapeutic efficacy and increases the risk of adverse events.[103,155]

LHMs are the perfect solution to these problems. They have a self-renewing lubrication layer, and liposomes coated on the surface of the hydrogel microspheres or inside the microspheres provide continuous lubrication during friction, thus

Table 3 Modification strategies for LHMs and related responsive materials

Response types	Modification strategy	Representative responsive materials
Temperature	Co-dissolve TSP in the organic phase	PNIPAAm (LCST $\approx$ 32 °C)
Magnetic	Physical encapsulation/embedding of MNPs	Fe_3O_4, FeO, Fe_2O_3, MO, BaO
pH	pH-sensitive lipid or polymer insertion	DOPE-CHEMS (pH-sensitive lipid)
Light	Direct insertion of photosensitizers into the phospholipid bilayer	BPD, Ce6, $AlPcS_2$, 5,10-DiOH
Immuno	Covalent coupling of antibodies *via* maleimide-thiol chemistry	Anti-HER2 cNB

TSP: temperature-sensitive polymer; LCST: lower critical solution temperature; ECM: extracellular matrix; MNPs: magnetic nanoparticles; cNB: camelid nanobody; DOPE-CHEMS: 1,2-dioleoyl-*sn-glycero*-3-phosphoethanolamine/cholesteryl hemisuccinate.

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reducing joint wear and tear while enabling sustained release of the drug and promoting cartilage repair (Fig. 5A and B).[120] Notably, Jahanmard *et al.*[156] embedded liposomes in GelMA microspheres using electrospray technology and found that the composite structure was able to withstand certain mechanical shear forces during surgical replacement. Research has shown that GelMA/liposomes increase pro-inflammatory cytokines, stimulate osteogenesis, and promote the differentiation of mesenchymal stem cells.

4.3 Wound repair

LHMs are gaining prominence in the field of wound repair owing to their versatile therapeutic potential.[73,157] In the management of chronic wounds, such as diabetic foot ulcers[158] and pressure ulcers,[159] LHMs have demonstrated efficacy in promoting accelerated wound healing while concurrently mitigating infection rates and reducing the likelihood of recurrence. In burn wound care, LHMs facilitate the establishment of a moist wound environment endowed with antimicrobial properties, thereby enhancing the epithelialization process. Furthermore, in post-surgical wound care, LHMs significantly diminish the risk of postoperative infections, underscoring their clinical utility.

Diabetic wounds tend to develop into complex and severe chronic wounds, which are difficult to treat, slow to heal and have numerous obstacles to the healing process, such as bacterial infections, ulcers, necrosis and other complications; liposomes combined with hydrogels and loaded with drugs can inhibit the inflammatory response and promote angiogenesis and tissue remodelling, thus speeding up the wound healing process.[92,160,161] Guo *et al.*[83] developed nanoliposomal composite hydrogel microspheres (PPD-Lipo@HMs) incorporating the natural active compound 20(*S*)-protopanaxadiol (PPD) through microfluidic technology. The PPD-Lipo@HMs demonstrated significant biological activity by stimulating vascular endothelial growth factor expression, thereby promoting endothelial cell migration, neovascularization, and tissue regeneration. Notably, the aggregation of PPD-Lipo@HMs forms microsphere folds that effectively cover damaged tissues, facilitating fibroblast and endothelial cell attachment, spreading, and proliferation. This unique structural feature contributes to the accelerated healing of diabetic wounds (Fig. 5C and D).

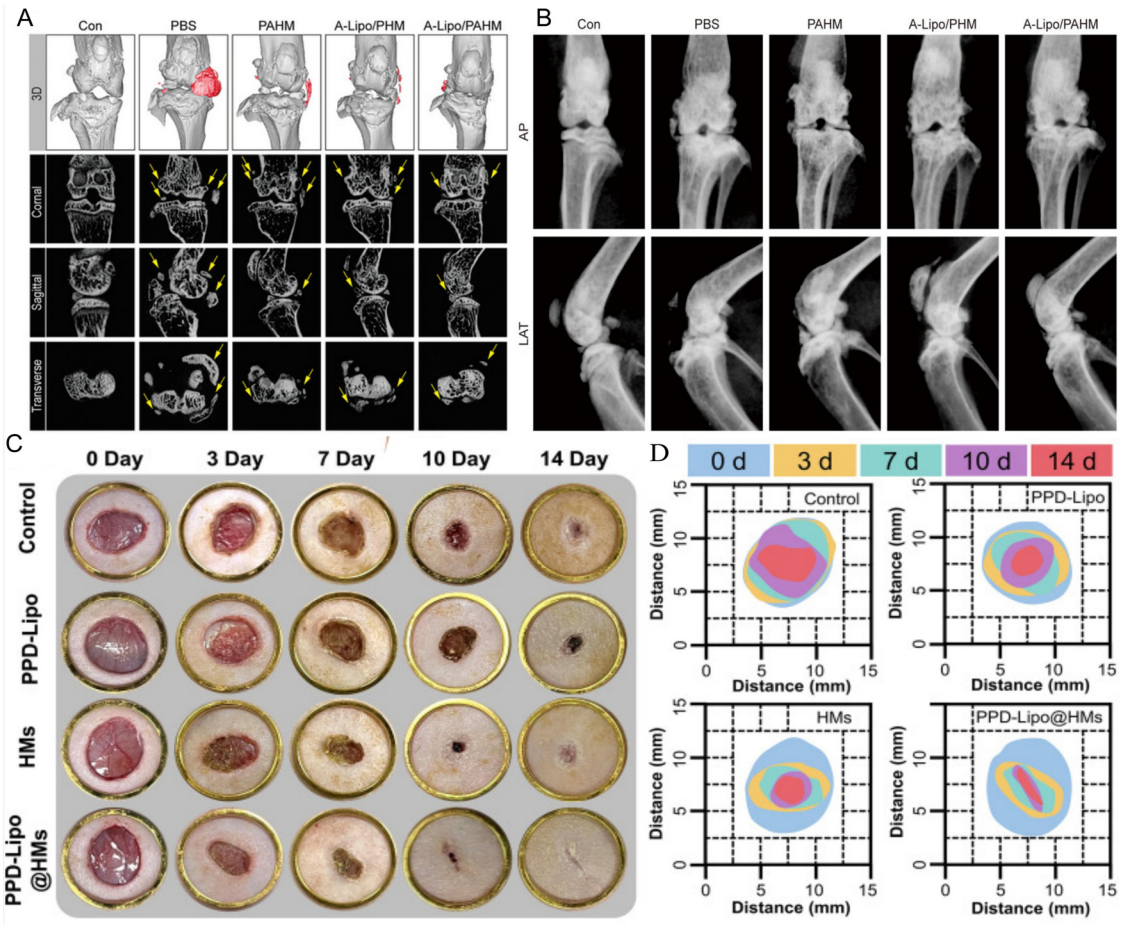

Fig. 5 Therapeutic potential of LHMs in bone and cartilage disorders, promoting wound healing in a full-thickness skin injury model of diabetic patients. (A) 3D reconstruction images, coronal, sagittal, and transverse images of the mouse knee microCT. (B) Representative X-ray films of the mice's knee joints in anterior-posterior and lateral views.[120] Copyright 2024. Reproduced with permission from Wiley. (C) Representative pictures of wound healing in different treatment groups on days 0, 3, 7, 10 and 14. (D) Schematic of the wound healing process.[83] Copyright 2024. Reproduced with permission from Spring Nature.

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4.4 Sensorineural hearing loss

Achieving safe and efficient drug delivery across the blood-labyrinth barrier to the inner ear remains a significant challenge in the prevention and treatment of sensorineural hearing loss. Hydrogel-based composite drug delivery systems have emerged as a promising solution, demonstrating dual capabilities of facilitating targeted inner ear delivery and overcoming the blood-labyrinth barrier restriction while maintaining sustained drug release.[162] Notably, injectable hydrogel microspheres (GM@PDA@Lipo-Ebselen) with bioadhesive properties have shown therapeutic efficacy through their adherence to the round window membrane in murine models. These microspheres effectively reduced reactive oxygen species production, mitigated mitochondrial dysfunction, and minimized the loss of hair cells and synaptic connections. Consequently, they demonstrated significant improvement in noise-induced hearing loss in murine subjects.[117]

4.5 Anti-tumour therapy

The primary challenges in drug-based tumor treatment include the high heterogeneity of tumor cells, immune evasion, and the development of drug resistance, as well as significant side effects and high treatment costs.[163] LHMs partially mitigate these issues. They can be utilized for localized tumor therapy by encapsulating antitumor drugs, enabling precise and sustained drug release, remodeling the tumor microenvironment, reducing systemic toxicity, and simultaneously increasing targeted drug concentrations to enhance therapeutic efficacy.[164,165]

The CRISPR/Cas9 nuclease system[166] is widely regarded as one of the most promising genome editing technologies for cancer therapy. Previous studies have often employed viruses for delivery; however, clinical translation remains a significant challenge when using viral vectors. To address this issue, Chen *et al.*[167] developed a novel composite delivery system comprising a polyethyleneimine hydrogel core and a cationic liposome shell. In this system, the polyethyleneimine hydrogel encapsulates the Cas9 protein, while the cationic liposomes deliver the genetic material. Leveraging the host–guest interaction between cyclodextrin and adamantane, a mechanically soft structure was constructed that effectively preserved protein activity. Notably, this composite delivery system demonstrated significant inhibition of tumor growth and a substantial reduction in tumor volume compared to the control groups.

4.6 Vaccine delivery

In clinical applications, vaccines face many challenges. Most synthetic peptides are poorly immunogenic and therefore require adjuvants to enhance their ability to stimulate an immune response; in addition, proteins are extremely sensitive to organic solvents, which may impair their natural antigenic properties, resulting in altered immunogenicity and adverse immune responses.[98,168] To address these limitations, we implemented an innovative approach by utilizing the LHMs drug delivery system for effective vaccine encapsulation and delivery.

Machluf *et al.*[78] developed an innovative vaccine delivery system by encapsulating recombinant hepatitis B surface antigen (HBsAg)-loaded liposomes within calcium alginate-based microspheres, which were subsequently surface modified with polylysine. Their experimental results demonstrated that this composite microsphere system effectively achieved sustained antigen release and maintained an antigen depot effect. Notably, this novel delivery platform significantly reduced the required vaccine dosage while eliminating the necessity for booster immunizations, thereby representing a promising approach for vaccine development.

For different diseases, either the modification of liposomes or the modification of hydrogels confers specific functions to the LHMs drug delivery system. This improves the efficiency of drug administration and avoids to some extent the shortcomings when used alone (Table 4).

5. Current challenges

LHMs, an advanced drug delivery system that integrates nanotechnology with hydrogel technology, demonstrate significant potential in the field of drug delivery. Nevertheless, several challenges persist in their practical applications.

5.1 High technical barriers

The preparation of LHMs is a complex and multifaceted process. Although liposome preparation and modification technologies are well-established, the fabrication of nanoscale hydrogel microspheres continues to face significant technical hurdles. For instance, microfluidic devices, which are inherently limited in scalability for large-scale batch production, often exhibit inconsistencies in performance, resulting in significant batch-to-batch variability.[72,117,169] The second critical aspect concerns the interfacial compatibility issue between liposomes and hydrogels. Beyond conventional integration approaches that involve either the encapsulation of liposomes within the hydrogel matrix or their surface adsorption onto hydrogel microspheres, establishing robust chemical bonding between drug-loaded liposomes and hydrogel microspheres while simultaneously endowing the system with precise environmental responsiveness remains a significant scientific challenge.[3,17]

5.2 High production costs

The fabrication of liposomes and their hydrogel-based composites necessitates the utilization of diverse essential raw materials. Liposome preparation predominantly employs phospholipids, cholesterol, and DSPE–PEG2000,[29] while hydrogel matrices are typically constructed using biomaterials, including gelatin,[103] GelMA[156] and chitosan.[122] The synthesis process further requires the use of organic solvents (*e.g.*, chloroform and methanol)[104] and crosslinking agents (*e.g.*, $CaCl_2$).[170] To confer intelligent responsiveness to the delivery system, specific modifications to either the liposomes or the composite microspheres are necessary,[20,41] which inevitably increases production costs. Therefore, the development of novel raw materials is crucial to reducing costs and streamlining the preparation process.

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Table 4 Modification strategies for LHMs and related responsive materials

Modification	Specific functions	Application
GelMA	Controlled-release	Osteoarthritis, bone injury
Sodium alginate	pH-sensitive	Myocardial injury
CMCS, HSA	pH-sensitive, enhance targeting	Hypercholesterolemia
BSPMA	Structural support and microenvironment regulation	Diabetic wound
Internalizing RGD	Enhance targeting	Tumor
Alginate-poly(L-lysine)	Controlled-release	Delivery of HBsAg

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5.3 Stability and safety issues

Liposomes, owing to their unique structural composition, exhibit high susceptibility to degradation by gastric acid, bile salts, and pancreatic lipase within the gastrointestinal tract following oral administration as drug delivery vehicles. This vulnerability often results in the structural disintegration of the liposomes and subsequent payload leakage.[171] In contrast, hydrogels demonstrate digestive behaviors that are predominantly governed by their compositional properties and the activity of specific digestive enzymes (*e.g.*, amylase, trypsin, pepsin, and pancreatic lipase). Furthermore, their performance in the gastrointestinal tract is influenced by variations in environmental parameters, including pH and ionic strength.[172] Drug-loading LHMs have significantly improved anti-digestive ability. However, as more materials are compounded, their safety becomes increasingly complex. Moreover, the storage conditions for LHMs may not be altered owing to the inherent nature of certain drugs. Consequently, it is particularly challenging to modify the storage conditions of the drug by altering the properties of the carrier while ensuring that the properties of the loaded drug remain unchanged.

5.4 Targeting and delivery efficiency

Although LHMs drug delivery systems demonstrate the potential for targeted drug delivery, their delivery efficiency and targeting accuracy in complex *in vivo* environments require further optimization in practical applications. Specifically, the distribution and residence time of these microspheres within the body must be fine-tuned to ensure precise drug delivery to lesion sites.[121,122] For example, for the treatment of disc degeneration, there is a need to ensure that LHMs can fully reach and act in the nutrient-restricted microenvironment of the disc. To cope with the complexity of the *in vivo* environment, LHMs can be designed for use in specific microenvironments. However, how to do this in a way that ensures accuracy at the lesion site is still a challenge.[173]

5.5 Intelligent response

LHMs have the following shortcomings in intelligent response: the response sensitivity is insufficient for accurate perception of environmental changes; the preparation process is complex, limiting large-scale production; and some materials are cytotoxic.[174–176] The following solutions can be adopted: optimize materials (*e.g.*, develop new temperature-sensitive polymers) to improve response efficiency; enhance stability through interfacial chemical bonding; simplify the process by employing modular design; and ensure safety by selecting non-toxic materials and conducting long-term toxicity studies.

To address these challenges, it is essential to optimize the composition and structure of liposomes to minimize the risks of rupture and fusion while exploring novel stabilizers or cross-linking agents to enhance the stability of both liposomes and hydrogels. The development of novel targeting ligands or modification methods aims to improve the targeting of LHMs. This includes thoroughly studying the distribution and retention mechanisms of microspheres *in vivo*, optimising delivery strategies, reducing the body's immune response and toxicity, conducting long-term toxicity studies and safety assessments, and ensuring the safety of the entire delivery system. Additionally, optimizing preparation processes and reducing costs involve researching new methods and equipment, improving production efficiency and product quality, using synthetic materials to replace traditional ones, lowering production costs and expanding applications. Introducing environmentally responsive hydrogels or modified liposomes into drug delivery systems, designing intelligent drug delivery systems that automatically adjust the release rate and dose of drugs in response to changes in internal and external environments, thereby improving the accuracy of treatment.

6. Conclusions and outlook

Liposomes, whether loaded with water-soluble or fat-soluble drugs, can be modified to significantly extend their circulation time in the bloodstream, thereby enhancing drug bioavailability and mitigating toxic effects. However, liposomes exhibit certain limitations. For instance, they are susceptible to degradation using the digestive system when administered orally. Furthermore, when directly injected into bone joints, liposomes fail to simultaneously achieve the dual objectives of slowing bone wear and controlling drug release. Hydrogels exhibit superior biocompatibility compared to liposomes. By immobilizing drug-loaded liposomes within the three-dimensional network of hydrogels through mechanisms such as physical adsorption, embedding, non-covalent interactions, or chemical cross-linking, the drug loading capacity and bioavailability are significantly enhanced. Moreover, the composite drug delivery system enables precise control and sustained release of therapeutic agents while effectively resisting digestive degradation, thereby significantly reducing the administration frequency.

LHMs represent a groundbreaking class of drug delivery systems with substantial research potential and promising applications. Advances in materials science and nanotechnology, coupled with ongoing technological innovation and practical

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experimentation, are expected to drive the evolution of these systems toward greater efficiency, safety, and intelligence. Consequently, LHMs are anticipated to gain broader adoption and promotion in the fields of drug delivery and tissue engineering.

Author contributions

The manuscript was written through contributions of all the authors. All the authors have given approval to the final version of the manuscript.

Conflicts of interest

On behalf of all the authors, the corresponding author states that there is no conflict of interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data and information presented in this review are based on previously published studies that are cited in the article.

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