REVIEW PAPER

Engineering of magneto liposomes to enhance theranostic biomedical applications

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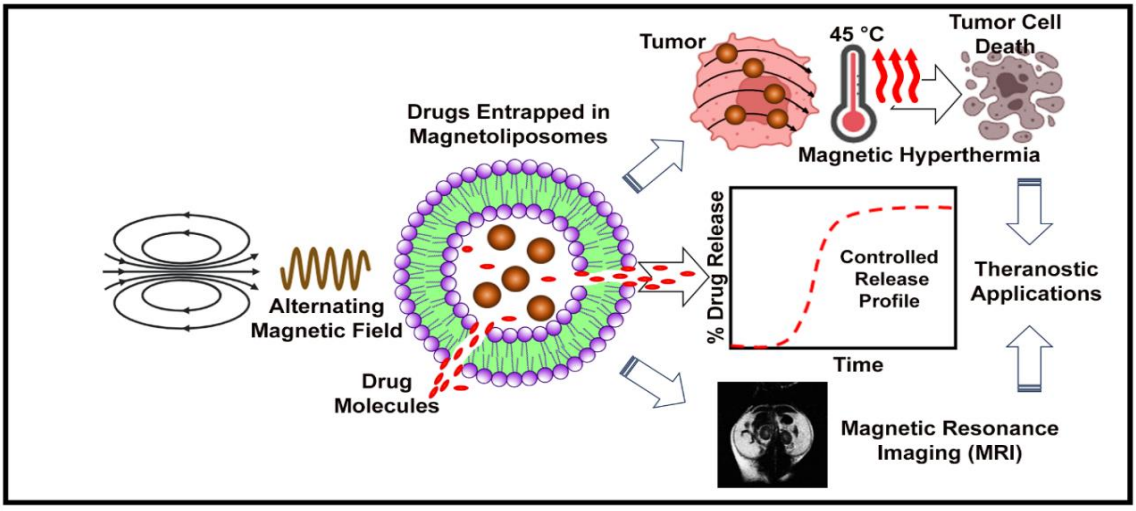
ABSTRACT

Magnetoliposomes, which are magnetically sensitive lipid nanocarriers, have garnered increasing attention in biomedical research due to their promising potential. Their biocompatibility and ability to transport therapeutic cargos with tailored physicochemical properties make lipid-based carriers, such as liposomes, highly valued in medical applications. In recent years, there have been significant advancements in integrating magnetic nanomaterials into medical technologies, particularly in areas such as magnetic resonance imaging (MRI) and therapeutic techniques like hyperthermic treatment, which targets and eliminates cancerous cells. This article provides an overview of the development of magnetically activated lipid nanocarriers, with a particular focus on magnetoliposomes in the medical field. The review examines the synthesis of magnetic nanoparticles and liposomes, the engineering of magnetoliposomes, and their applications in healthcare. Furthermore, the article examines synthesis techniques in detail, offering insights into the complex interactions between magnetic materials and lipid carriers. The synergistic combination of magnetic elements and lipid nanocarriers is driving a paradigm shift in medicine, offering the potential to revolutionize both diagnostic and therapeutic interventions.

Keywords: *SPION; Liposomes; Drug delivery; Magnetic nanoparticles; Theranostics*

How to cite this article
Durgadevi P, Girigoswami K, Bose D, Thirumalai A, Harini K, Kiran V, Girigoswami A. Engineering of magnetoliposomes to enhance theranostic biomedical applications. Nanomed J. 2026; 13(1): 1-29. DOI: 10.22038/NMJ.2025.82865.2068.

Graphical Abstract



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Note. This manuscript was submitted on September 26, 2024; approved on May 03, 2025.

INTRODUCTION

Liposomes are spherical, bi-layer lipid vesicles with an enclosing aqueous phase, capable of encapsulating a variety of compounds [1, 2]. Liposome-encapsulated drugs exhibit improved stability, solubility, and bioavailability *in vivo*, enhancing their pharmacokinetics and biodistribution while reducing toxicity [3]. Due to their biocompatibility, ability to control the pharmacokinetics of encapsulated drugs, and targeted tissue delivery, liposomes have garnered significant attention in biomedicine over the past few years. They possess remarkable versatility, enabling the encapsulation of both hydrophobic and hydrophilic compounds by utilizing the unique amphiphilic properties of the lipids used in their formulation. This capability allows liposomes to effectively carry drugs with poor water solubility, providing a promising strategy for enhancing drug delivery in various therapeutic applications [4]. A variety of substances, including antibodies, aptamers, carbohydrates, peptides, and proteins, can be used to functionalize the surface of liposomes for targeting diseased cells. Several polymers have been explored as stabilizers for fragile liposomes, with polyethylene glycol (PEG) gaining significant attention in the development of nano-enabled drug delivery systems [5]. PEG-coated liposomes have been shown to remain in circulation longer than their uncoated counterparts. In addition to the prolonged circulation time, the enhanced permeation and retention (EPR) effect further improves the passive targeting of anticancer drugs by extending the exposure of tumor cells to the drugs [6]. Incorporating specific lipids into liposomes that are sensitive to stimuli such as temperature, redox conditions, pH, or light can create stimuli-responsive systems for controlled drug release [7]. Furthermore, inorganic nanoparticles have been incorporated as additives to enhance responsiveness to external magnetic fields or light, facilitating the targeted release of drugs at the diseased site.

Superparamagnetic iron oxide nanoparticles (SPIONs), with specific size ranges and surface properties, are gaining increasing attention as a particular class of nanoparticles, especially when incorporated into liposomal structures [8, 9]. SPIONs have a wide range of biomedical applications, including serving as nanocarriers for targeted drug delivery, acting as MRI contrast agents, and being utilized in hyperthermia-based cancer treatments. The inclusion of SPIONs in lipid materials enables a magnetic response, allowing these materials to be remotely controlled and activated by an external magnetic field [10]. In addition to their use in imaging and cancer ablation therapy, magnetic materials are also being explored for triggered release functions in biomedicine. The primary goal of creating lipid-SPION assemblies is to open new avenues for biological applications, particularly in scenarios where other stimuli may be limited. These assemblies offer a promising approach to utilizing magnetically activated lipid nanocarriers, which could potentially address the limitations of other activation methods. This innovation presents exciting prospects for targeted drug delivery and other theranostic applications, where precise control over carrier behavior is essential [11]. The use of SPIONs as MRI contrast enhancers has proven highly effective in medical imaging. MRI works by detecting the unpaired nuclear spins of hydrogen atoms exposed to an external magnetic field, and SPIONs have been shown to function well as contrast agents in this technique [12, 13]. Due to the high spatial resolution of MRI, it does not require high-energy radiation, and the magnetic field can penetrate deep into tissues, minimizing the need for excessive radiation. MRI is utilized in a wide range of applications, including cancer diagnosis, biodistribution monitoring, and imaging of tumor vasculature [14]. While MRI can track drug delivery systems and visualize pharmacokinetic and digestive processes, its ability to distinguish diseased tissue from surrounding healthy tissue remains limited [15]. Therefore, contrast enhancement is often necessary to improve the visualization of target tissues, typically achieved by using gadolinium-containing chelate complexes [16]. However, due to the potential toxicity of free gadolinium, the use of SPIONs for contrast enhancement has gained popularity due to their established biocompatibility.

A magnetic field can guide magnetically sensitive drug carriers to specific tissue sites, enabling them to accumulate at the desired location for drug delivery. When magnetic particles containing anticancer agents are administered intravenously, applying an external magnetic field to the tumor site has been shown to attract and concentrate these particles in vivo. This approach is valuable for improving formulations and minimizing the distribution of harmful drugs to healthy tissues. The magnetic nanoparticle-based targeting strategy can also be combined with other stimuli-sensitive mechanisms, such as SPIONs loaded into specific drug delivery systems, enabling magnetically guided targeting followed by near-

infrared (NIR)-triggered drug release on demand [17]. Magnetic hyperthermia has emerged as a promising cancer treatment due to its ability to generate heat within tumor cells. Heat stress, induced when cells are exposed to temperatures above 43-45°C, activates several intracellular and extracellular degradation mechanisms, including protein folding, denaturation, and aggregation [18, 19]. By locally increasing the temperature at the lesion site, apoptosis of tumor cells can be induced. The use of superparamagnetic nanoparticles is particularly advantageous in hyperthermia, as an alternating magnetic field can stimulate heat generation externally. Several factors have been shown to critically influence the heating efficiency of superparamagnetic nanoparticles, including particle size, size distribution, shape, concentration, and the strength and duration of magnetic field activation. While SPION-based hyperthermia and SPION-driven MRI have been extensively studied for cancer treatment, no commercial products have been developed to date, and preclinical research is still ongoing [20].

This review article aims to provide an overview of the current status of lipid-based nanocarriers, such as liposomes, in combination with superparamagnetic nanoparticles and their applications in the healthcare industry. The synthetic procedure and controlled drug release mechanism are addressed on a priority basis.

Magnetic nanoparticles

Two major factors determine whether nanoparticles exhibit magnetic properties: their finite size and surface properties. The specific surface effects arise from the breaking of symmetry at the boundary of each magnetic nanoparticle, while quantum confinement of electrons is the primary cause of finite-size effects [21]. These finite-size effects in magnetic nanostructures can be classified into two types: the single-domain limit and the superparamagnetic limit. Larger magnetic particles typically possess a multidomain structure, where domain walls separate regions with uniform magnetization. A domain wall forms when the domain wall energy (E_{dw}) balances with the magnetostatic energy (ΔE_{MS}) [22]. As the particle size decreases to a specific critical volume, a point is reached where the energy required to create a domain wall exceeds the energy needed to interact with the stray magnetic field or the external magnetostatic energy when the system is in a single-domain state. This threshold, known as the critical diameter, is influenced by the material's properties and typically falls within a range of tens to hundreds of nanometers. The exact value of the necessary diameter varies depending on factors such as the material's magnetic characteristics and the surrounding environmental conditions. The estimated single-domain size or critical diameter of spherical particles for Fe, Ni, Fe_3O_4, HCP Co, and FCC Co are 15, 55, 128, 15, and 7 nm, respectively [23].

In a single-domain particle, the spins are aligned in the same direction, and the particle is uniformly magnetized. Since there are no domain walls to shift during spin rotation, the magnetization is reversed through spin rotation. As a result, magnetic coercivity is very high in small nanoparticles. The high coercivity of nanoparticles also depends on their shape anisotropy [24]. An isolated single-domain particle serves as a good model for understanding superparamagnetism. Energy barriers separate two magnetization directions that are energetically equivalent. The magnetization of the nanoparticles can easily flip when the thermal energy of the particles exceeds the energy barrier, a phenomenon that becomes more prominent with decreasing size [21]. Therefore, the nanoparticles behave as superparamagnets rather than exhibiting atomic magnetic moments. These particles exhibit no hysteresis, as their magnetic moments align parallel to one another, resulting in no residual magnetization or coercive field [25].

Magnetic nanoparticles (MNPs) have the potential to revolutionize clinical diagnostics and therapeutics [26, 27]. Researchers are actively investigating MNPs due to their unique physicochemical properties, which enable them to function at both the cellular and molecular levels. To harness magnetic phenomena at the nanoscale, such as enhanced magnetic moments and superparamagnetism, various MNPs with different chemical compositions have been proposed and evaluated [28]. In nanotechnology, the critical properties of fine particles can now be precisely engineered, similar to other nanomaterial-based systems. A range of processes is available to tailor the surface chemistry, composition, size, and morphology of nanoparticles to enhance their magnetic properties and control their behavior *in vivo* [29]. MNP platforms for biomedical applications typically consist of an inorganic nanoparticle core and surface functionalization that stabilizes them under physiological conditions. This fabrication enables MNPs to perform multiple functions simultaneously, including multimodal biomedical imaging, drug delivery, and real-time monitoring of therapeutic progress or disease progression, ultimately enhancing patient care. Nanomedicine offers promising applications, including the

enhancement of proton relaxivity in specific tissues, positioning MNPs as potential contrast agents for MR imaging [30]. The use of MNPs as MR imaging contrast agents, particularly in the form of SPIONs, has been studied for over three decades.

To improve the resolution of MR imaging for disease diagnosis, contrast agents are used to shorten either the longitudinal (T1) or transverse (T2) relaxation times of hydrogen or water protons, thereby enhancing the contrast. Positive contrast enhancement is achieved with T1 contrast agents, resulting in a brighter image, while negative contrast enhancement is achieved with T2 contrast agents, yielding a darker image [31]. Due to the Blooming effect, T2 contrast agents are inherently more susceptible to producing long-range magnetic fields that disturb neighboring tissues and distort the background image [32]. Due to the Blooming effect and the presence of bleeding areas, calcifications, and metal deposits, the location of T2 contrast agents can be easily misidentified. In contrast, T1 MRI contrast agents, such as paramagnetic ions, do not alter the magnetic homogeneity or affect the anatomical background, allowing for the generation of a clear T1 contrast image in MRI. Because of the limitations of T2 contrast agents, T1 contrast agents, particularly gadolinium chelates like Gd-DOTA (gadolinium-labeled 1,4,7,10-tetraazacyclododecane-tetraacetic acid) or Gd-DTPA (gadolinium-labeled diethylenetriamine pentaacetic acid), are more commonly used in clinical settings than T2 contrast agents [33]. A substantial amount of attention has been focused on SPIONs due to their intrinsic magnetic properties, biocompatibility, biodegradability, and ability to significantly shorten transverse relaxation times. Additionally, SPIONs are minimally toxic, have long blood half-lives, and possess tunable surface chemistry. The FDA has approved several formulations of SPIONs as T2-weighted contrast agents due to their effectiveness in clearing the body after imaging and their natural degradation mechanisms. SPIONs are widely used in the clinic as a bowel contrast agent (Lumiren and Gastromark), liver and spleen imaging agents (Feridex IV and Endorem), and as a lymph node contrast agent (Combidex), which consists of ultra-small superparamagnetic iron oxide (USPIO) nanoparticles [34, 35].

Synthetic routes of magnetic nanoparticle preparation

Various compositions and phases have been used to synthesize magnetic nanoparticles, such as iron oxides (Fe_3O_4, γ-Fe_2O_3), $MgFe_2O_4$, $MnFe_2O_4$, $CoFe_2O_4$, $CoPt_3$, FePt, and others. To synthesize high-quality magnetic nanoparticles, several popular techniques are available, including coprecipitation, thermal reduction and decomposition, microemulsions, micelle-based synthesis, reverse micellar synthesis, hydrothermal synthesis, and laser pyrolysis.

Coprecipitation synthesis

Coprecipitation, or the addition of a base under an inert or nitrogen atmosphere at room temperature or elevated temperatures, is a simple and efficient method for synthesizing iron oxide nanoparticles from aqueous Fe^{2+} and Fe^{3+} salt solutions (equation-i) [36]. The physicochemical properties, including size, shape, and magnetic behavior, of nanoparticles synthesized using this method primarily depend on the composition of the salts used, such as chloride, nitrate, sulfate, etc. Other significant parameters that influence the physicochemical behavior include the ionic strength and pH of the reaction medium, reaction temperature, and the molar ratio of Fe^{2+} to Fe^{3+} [37]. When the conditions for synthesis are optimized, reproducible quality magnetite nanoparticles can be obtained once the synthetic process is established. Experimental measurements have determined that the magnetic saturation values range between 30 and 50 emu/g, which is lower than the bulk value of 90 emu/g for magnetite nanoparticles [38]. The primary issue with this synthetic procedure is the stability of the synthesized magnetite nanoparticles. Magnetite nanoparticles are easily oxidized to maghemite under normal conditions and readily dissolve in acidic media. Oxidation is less of a concern in maghemite, as it is ferrimagnetic. Therefore, magnetite particles can be converted to maghemite by deliberate oxidation. The resulting maghemite particles remain chemically stable in both alkaline and acidic media after dispersion in an acidic medium and the addition of Fe^{3+} nitrate.

$$aq.\,Fe^{2+} + aq.\,Fe^{3+} + aq.\ OH^{-}[NaOH/NH_3OH/N(CH_3)_4OH] \xrightarrow{Reduction} Fe_3O_4 \quad \text{(i)}$$

Co-precipitating Fe_3O_4 is experimentally challenging, as particle size must be precisely controlled to achieve a uniform particle size distribution, even if magnetite is converted to maghemite after initial formation. As a result of coprecipitation, the particles are generally polydisperse. However, producing monodisperse particles requires a rapid nucleation burst followed by a controlled, slower growth pattern. To achieve monodisperse iron oxide nanoparticles, it is essential to control these processes. In recent

years, organic additives such as surfactants or polymers have been employed to stabilize nanoparticles, facilitating the synthesis of monodisperse magnetite nanoparticles in a range of sizes [39]. Maghemite nanoparticles of varying sizes were prepared by forming magnetite in an alkaline medium in the presence of trisodium citrate, followed by oxidation with Fe^{3+} nitrate at 90°C for 30 minutes. The particle size was controlled from 2 nm to 8 nm by varying the Fe^{2+}/Fe^{3+} ratio [40]. Various organic anions, including carboxylates and hydroxy carboxylates, have been studied for their effects on controlling the size and stability of iron oxides or oxyhydroxides. In systems with few nuclei, where particle growth dominates, chelation of metal ions prevents nucleation, resulting in larger particles. Additionally, additives may adsorb onto nuclei and growing crystals, inhibiting particle growth and favoring the formation of smaller particles [41]. Several studies have shown that Fe_3O_4 is most effectively stabilized by oleic acid

Microemulsion-based synthesis

Chemical reactions in restricted geometries can be conducted using microemulsions, a method for producing nanomaterials. Microemulsions are thermodynamically stable, isotropic dispersions of immiscible liquids, where the interfacial film of surfactants stabilizes the microdomains of these liquids. The oil (O)-water (W) interface accumulates surfactant molecules that stabilize the microemulsions by dispersing nanometer-sized water droplets into the oil or organic medium [42]. A droplet nanoreactor is primarily used to prevent phase separation by creating a compartmentalized medium. The size of the nanoreactors, or reversed micelles, can be precisely controlled by adjusting the molar ratio of water to surfactant. In addition to lowering the surface tension of the O/W interface, surfactants also alter the entropy of the system, thus influencing the free energy of microemulsion formation. Due to the large number of very small droplets formed in a microemulsion, the change in interfacial area is significant. The large number of small droplets formed by mixing two phases results in a substantial favorable entropic contribution. This, in turn, leads to a significant reduction in surface tension and a favorable entropic change, resulting in negative free energy of formation [43]. In such cases, spontaneous microemulsification leads to a thermodynamically stable dispersion, and the practical interaction volume of O/W droplets is naturally larger than that of W/O droplets.

In a microemulsion, soluble metal salts are contained in aqueous microdroplets surrounded by oil in the aqueous phase [44]. Continuous collisions, coalescence, and breakup occur between these microdroplets, leading to the formation of a precipitate within the micelles when two identical microemulsions of water in oil, containing the desired reactants, are mixed. This process produces finely dispersed precipitates that can be separated from the surfactants by centrifugation or the addition of organic solvents. Aerosol-OT/n-hexane reverse micelles have been used to synthesize highly monodisperse iron oxide nanoparticles [45]. Hydrophilic compounds and salts are dissolved in the aqueous inner core of reverse micelles. In n-hexane, reverse micelles are formed by AOT, containing an aqueous core of deoxygenated Fe^{3+} and Fe^{2+} salts. The precipitation of magnetite at low temperatures, in the presence of nitrogen or an inert gas, is achieved chemically using a deoxygenated sodium hydroxide solution. Reverse micelles of cetyltrimethylammonium bromide (CTAB) have been used to synthesize metallic Co, Co/Pt alloys, and Au-coated Co/Pt nanoparticles, with 1-butanol as the cosurfactant and octane as the organic medium (oil) [46]. Sodium dodecylbenzenesulfonate is used as a surfactant to form W/toluene inverse micelles containing $MnFe_2O_4$ nanoparticles of varying sizes, ranging from 4 to 15 nm. An aqueous solution of manganese nitrate and ferrous nitrate is prepared for this synthesis. Sodium dodecylbenzenesulfonate is added to the solution, followed by toluene to form reverse micelles. The volume ratio between water and toluene determines the size of the $MnFe_2O_4$ nanoparticles. For the synthesis of cobalt ferrite, precursor salts of iron(III) and cobalt(II) are mixed in deionized water in a 2:1 ratio and gradually added in stoichiometric amounts to a solution of surfactant, n-hexane, and butanol (1:1). The reaction mixture is continuously stirred for 20 hours. At this stage, a NaOH solution is added dropwise to the microemulsion to adjust the pH to 10. Finally, 7 ml of triethylamine is added to the mixture at 80°C to obtain a slurry of cobalt ferrite nanoparticles [47].

Thermolysis or thermal decomposition

The thermal decomposition of organometallic compounds with stabilizing surfactants in organic or nonaqueous solvents can be used to synthesize monodisperse magnetic nanocrystals with smaller sizes. Metal acetylacetonates, metal cupferronates (Cup = $C_6H_5N(NO)O^-$), and metal carbonyls are common organometallic precursors used with

surfactants such as oleic acid, various fatty acids, and hexadecylamine in the synthesis of magnetic nanomaterials via thermal decomposition [44]. Several factors play a crucial role in controlling the size and morphology of magnetic nanoparticles, including the ratio of starting reagents (organometallic compounds, surfactants, and solvents). To precisely control size and morphology, it is also critical to consider the reaction temperature, reaction time, and aging period. Rockenberger reported that in the presence of octylamines and trioctylamines, monodisperse maghemite was generated by the decomposition of iron cupferronates [48].

The formation of oxide nanoparticles can also be achieved through two-step procedures when the metal in the precursor is zero-valent, as in carbonyls. For example, using a precursor that contains zero-valent metals, such as $Fe(CO)_5$, high-quality, monodisperse iron oxide magnetic nanoparticles can be obtained by initially forming metallic nanoparticles, followed by oxidation [49]. Through the thermal decomposition of iron acetylacetonate, cobalt acetylacetonate, and manganese acetylacetonate, Sun et al. prepared ferrite magnetic nanomaterials with monodispersity [50]. By adding bipolar surfactants to hydrophobic nanoparticles, the authors introduced a simple method to make them hydrophilic. They also prepared iron-platinum monodispersed nanoparticles using a similar approach, which involved reducing platinum acetylacetonate, followed by the thermal decomposition of $Fe(CO)_5$, and then adding oleic acid and oleylamine [51]. Using dibenzyl ether, 1,2-dodecanediol, oleic acid, and oleylamine, Asghar et al. synthesized manganese ferrite ($MnFe_2O_4$) nanoparticles by dissolving iron and manganese acetates (2:1 molar ratio) and subsequently subjecting the mixture to thermal decomposition at 350°C [52]. Peddis and coworkers synthesized oleic acid-coated $CoFe_2O_4$ nanocrystals with a narrow size distribution and a self-assembling arrangement. They used the thermal decomposition of iron(III)-acetylacetonate and cobalt(II)-acetylacetonate in the presence of oleylamine, 1,2-hexadecanediol, oleic acid, and phenyl ether, heating at 200°C and 265°C for 30 minutes separately [53]. Jana et al. described an approach based on the pyrolysis of metal fatty acid salts in nonaqueous solutions to synthesize size- and shape-controlled magnetic oxide nanocrystals [54]. The reaction system consisted of a hydrocarbon solvent, fatty acids, metal fatty acid salts, and an activation reagent.

Hydrothermal synthesis

One of the most promising and environmentally friendly methods for synthesizing magnetic nanomaterials is the hydrothermal procedure, which is widely recognized. Hydrothermal synthesis, also known as solvothermal synthesis, is a heterogeneous chemical reaction that utilizes high pressure and temperature to synthesize materials in an aqueous solution [55]. This method eliminates the need for hazardous and expensive chemicals and produces fewer by-products than other methods. The hydrothermal process offers several advantages, the most important being the ability to prepare magnetic nanoparticles with reactive surface groups in a one-pot process, which can then be functionalized for various biomedical applications. Several factors influence the properties of the final products, including particle size, crystallinity, and magnetic properties. These factors include the reaction temperature, reaction time, choice of oxidation agents, stabilizing agents, and solvent [56]. The crystallinity of the synthesized Fe_3O_4, derived from ferrous chloride and diamine hydrate, improved as the temperature increased from 100°C to 180°C. This led to sharper and narrower reflection peaks in the XRD pattern, as reported by Wang et al. [57]. Additionally, particles with longer reaction times were found to be larger, as calculated using the Debye-Scherrer equation. For Fe_3O_4 nanoparticles synthesized at a higher temperature (140°C), the saturation magnetization (M□) was approximately 85.8 emu/g, significantly higher than the saturation magnetization of Fe_3O_4 nanoparticles synthesized at 100°C (12.3 emu/g). The enhanced magnetic property is likely due to the improved crystallinity of the particles.

Karaagac et al. optimized the synthesis conditions for manganese ferrite magnetic nanoparticles using the hydrothermal method [58]. The samples synthesized at 120°C exhibited two different forms, while higher temperatures led to the formation of two additional components: hematite and maghemite. When the reaction temperature was increased to 130°C, the pure manganese ferrite phase was obtained. As the reaction temperature and time were increased, the particle size grew from approximately 16.1 to 25.8 nm and from 19.4 to 25.8 nm, respectively. They also reported that as the reaction temperature and time increased, the saturation magnetization (M□) of manganese ferrite also increased, with pure manganese ferrite nanoparticles having an M□ of

approximately 65 emu/g at low temperatures and longer reaction times [58]. Due to strong dipole-dipole interactions and van der Waals forces between particles, magnetic nanoparticles tend to aggregate. It has been demonstrated that an external magnetic field can induce the aggregation of magnetic nanoparticles, thereby reducing their dissolution rate, which may significantly impact their relaxivities during magnetic resonance imaging (MRI) and their contrast efficiency. Therefore, surface functionalization of magnetic nanoparticles, such as Fe_3O_4, is essential for enhancing their colloidal stability. Hydrothermal methods offer better opportunities than other synthetic routes in this regard. Surface functionalization also enhances their biocompatibility and bioavailability for biomedical applications [59, 60].

The hydrothermal method has several disadvantages, including the high cost of the hydrothermal autoclave and setup, safety concerns during synthesis, and the requirement to maintain high temperatures and pressures. Microwave-assisted hydrothermal or hybrid hydrothermal methods are widely used for the synthesis of high-crystallinity composite materials with higher purity levels [61]. Water solubility at the desired pressure is a crucial factor in the synthesis of hydrothermal-based nanomaterials, and Teflon-lined stainless steel autoclaves are used to maintain the reaction conditions. These autoclaves maintain a specific temperature that induces internal pressure, allowing the precursor to dissolve and react, followed by the growth of nanocrystals. By combining hydrothermal synthesis with microwaves, the reaction kinetics can be enhanced. Since the entire reaction occurs in a closed system, it is environmentally safe, faster, and more energy-efficient. Sreeja et al. reported that microwave-hydrothermal synthesis produces nanosized γ-Fe_2O_3 [62]. The average particle size of the powdered magnetic nanoparticles was estimated to be 10 nm based on XRD and TEM studies. A superparamagnetic nature and a superparamagnetic blocking temperature of 200 K at room temperature were determined for γ-Fe_2O_3 nanoparticles based on magnetometry studies. As reported by Alkhayal et al., the microwave-hydrothermal method was used to synthesize cube-like magnetic Fe_3O_4 nanocomposites with reduced graphene oxide [63]. By varying the reaction time, pressure, and microwave power, they were able to control the shape and size of the magnetic nanocomposites, with the size of the SPION nanocomposites restricted to 24–34 nm.

Electrochemical synthesis

Several challenges arise during the synthesis of aqueous magnetic nanoparticles, including controlling particle size, reducing polydispersity, preventing aggregation, and maintaining particles within the nanometer scale. To address these issues, magnetic nanoparticles have been dispersed in polymeric solutions or inorganic matrices to create nanocomposites [64]. However, preparing colloidal suspensions of these amorphous powders for biomedical applications remains difficult. While synthesis in organic media produces homogeneous magnetic nanoparticles, the hydrophobicity of the particles presents challenges in biological applications. Among the conventional methods for producing magnetic nanoparticles, electrochemical synthesis is emerging as an alternative. The fundamental principle behind electrochemical synthesis involves passing electricity between two electrodes (anode and cathode) while they are immersed in an electrolyte [65]. A metal ion is formed in the electrolyte by oxidizing the anode, followed by reduction to metal at the cathode with the aid of stabilizers. A coating or thin metal film is typically deposited on the electrode. Additionally, coatings can be grown on substrates with varying morphologies due to the solid-liquid interfaces (electrode-electrolyte). Uniform polarization can be achieved by using a counter electrode with the appropriate shape and orientation. This method requires that neither the temperature nor the boiling points of the electrolyte be exceeded. Thermodynamic control of the electrolytic reaction can be achieved by adjusting the cell potential, while kinetic control is achieved by changing the current passing through the cell [66].

This method offers several advantages, including the ability to adjust the current density and electrode potential of the electro-oxidation process to control particle size. Surfactant molecules can also be used to prevent particle aggregation if they are included during synthesis. This approach for generating Fe_3O_4 nanoparticles in the size range of 20–30 nm has gained attention, as conventional methods often fail to achieve this size [67]. Hammed et al. developed a tubular electrochemical system to scale up the synthesis of superparamagnetic Fe_3O_4 nanoparticles [68]. The system achieved a production capacity of 8.3 mg/ml Fe, with a rate of 163 µg/mol Fe per minute, and the gradual supplementation of electrolytes resulted in a 75% higher yield. Mazario et al.

reported the facile synthesis of polydopamine-coated magnetite nanoparticles through iron electro-oxidation in an aqueous solution of dopamine [69]. An oxidative and alkaline environment is used to initiate the self-polymerization of dopamine with magnetite nanoparticles during the synthesis process. The addition of dopamine at various stages of synthesis allows for control over the size of magnetite nanoparticles and their polydopamine coatings. The core size ranges from a few nanometers to 25 nm, while the shell size achieved by this method is approximately 5 nm. In their work, Yu et al. used a one-step cathode glow discharge electrolysis plasma technique to fabricate Fe_3O_4 magnetic nanoparticles [70]. The resulting products had particle sizes of less than 20 nm. Pawar et al. applied an electrochemical method to synthesize citric acid-stabilized iron oxide nanoparticles for the adsorption of Congo red [71]. While electrosynthesis offers advantages, it also has some drawbacks. Because it is performed at room temperature, it often results in poorly ordered particles. Additionally, electrodeposition can only be conducted on conductive substrates, and XRD analysis typically reveals an amorphous structure, indicating the presence of impurities. Despite these limitations, electrosynthesis can still produce metastable phases of magnetic nanoparticles, such as iron oxide nanoparticles, due to its unique characteristics as a "soft chemistry" method.

Colloidal liposomes

Liposomes are colloidal drug transporters, typically ranging from 25 nm to 5.0 µm in diameter, that form spontaneously when specific lipids are hydrated in an aqueous medium [72, 73]. These colloidal structures consist of one or more bilayers made from natural or synthetic lipids, which enclose an aqueous volume at the core (Figure 1). Pharmaceutics with a wide range of lipophilicities can be encapsulated in liposomes, either in the aqueous core, within the bilayers made of phospholipids, or at the bilayer interfaces. Hydrophilic molecules prefer to reside inside the aqueous core, hydrophobic molecules bind to the lipid domain, and amphiphilic molecules or drugs become integrated into the membrane structure. Liposomes or extracellular vesicles are classified based on their lamellarity and compartment structure, such as ULV (unilamellar vesicle), OLV (oligolamellar vesicle), MLV (multilamellar vesicle), and MVV (multivesicular vesicles) or MVP (multivesicular liposomes), as shown in Figure 1 [73]. ULVs are spherical vesicles with a single phospholipid bilayer, subdivided into SUV (small unilamellar vesicle, size < 50 nm), LUV (large unilamellar vesicle, size > 50 nm), and GUV (giant unilamellar vesicle, size 10 to 100 µm). OLVs (size 2 to 4 µm) are a specific type of vesicle with a few concentric lamellae [74]. MLVs (size 0.5 to 5.0 µm) are formed by mechanically dispersing dry lipids in an aqueous solution, resulting in multiple concentric bilayers separated by narrow aqueous channels. MVVs are micron-sized vesicle-in-vesicle colloidal systems, where numerous vesicles are arranged non-concentrically [75, 76].

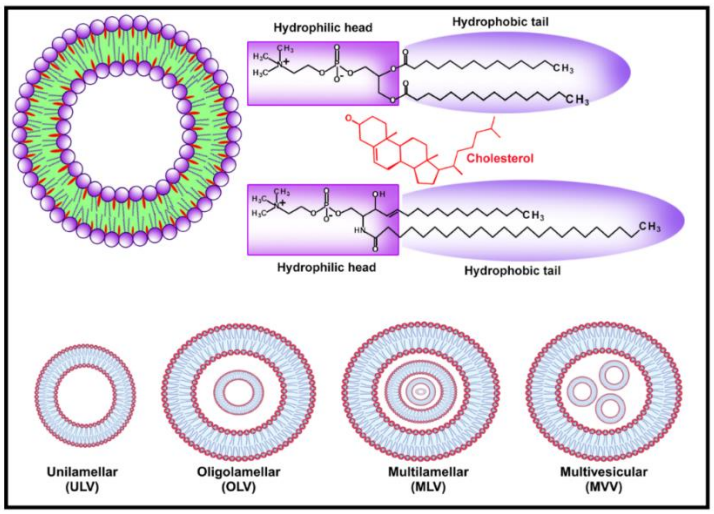

Fig. 1. Lipid- and cholesterol-based liposome structure fabrication in an aqueous solution, including classifications based on the lamellarity

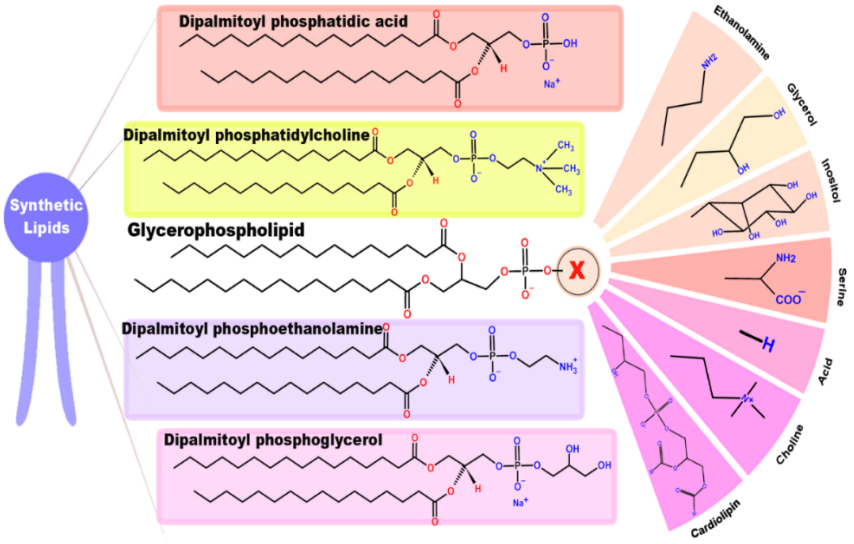

Fig. 2. Commonly used phospholipids for the preparation of liposomal nanoformulations.

Liposomal structures are similar to cell membranes, as they are composed of phospholipids that can spontaneously form vesicular structures upon hydration. This is due to the presence of an amphiphilic molecular structure consisting of a hydrophilic head group and a hydrophobic tail (fatty acid chains) [77]. The common phospholipids (PL) include glycerophospholipids, sphingolipids, and cholesterol (Figure 2). Phosphatidic acid, phosphatidylserine, phosphatidylglycerol, and cardiolipin head groups impart a negative charge on liposomes, while phosphatidylcholine and phosphatidylethanolamine are responsible for the neutral head groups at physiological pH. Synthetic lipids, such as DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphocholine), DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), MPPC (1-myristoyl-2-palmitoyl-sn-glycero-3-phosphocholine), DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine), POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine), and DPhyPC (1,2-diphytanoyl-sn-glycero-3-phosphocholine), have gained significant interest today (Table 1). The incorporation of cholesterol shapes the liposomes to resemble the plasma membrane, stabilizing them as drug delivery vehicles by controlling elasticity, fluidity, and permeability. Cholesterol content is a critical variable that can affect the size and integrity of liposomes [78]. Cholesterol enhances the compaction of phospholipid molecules within the bilayer, reducing bilayer permeability to both non-electrolyte and electrolyte solutes (Figure 1). Additionally, it strengthens vesicle resistance to aggregation and modifies the fluidity of intravesicular interactions, making them more rigid. Cholesterol also helps the lipid bilayer withstand severe shear stress, although this comes at the expense of reduced drug incorporation efficiency [79]. Reconstituted bilayers can incorporate up to 50 mol% cholesterol, which is typically considered the maximum amount [80]. However, the precise ratio of cholesterol to lipid required for achieving a more stable and efficient formulation remains unclear. Commonly used ratios include 2:1 (lipids: cholesterol) or 1:1 [81].

Table 1. Phospholipids used in the liposomal formulations with their applications

Sl. No.	Liposomal formulations	PL-used	Encapsulated materials	Applications	Ref.
1.	Drug-entrapped bi-functionalized thermosensitive liposomes	DPPC, DSPC, MPPC, DSPE-PEG_{2000}	SPION & DOX	Drug delivery system (DDS) to cross BBB for the treatment of glioblastoma multiforme (GBM)	[82]
2.	Iridium-polypyridyl-complexes encapsulated liposomes	PC-98T-DSPE-$MPEG_{2000}$	Iridium-polypyridyl-complexes	Induce apoptosis and inhibit polymerization of microtubules	[83]
3.	Nanobowl-supported liposomes	DSPE-$MPEG_{2000}$ and DSPC	DOX	Antitumor DDS	[84]
4.	Amino acid-conjugated liposomes	Soybean phospholipid	Drug/fluorescent marker	Pancreatic cancer therapy	[85]

Sl. No.	Liposomal formulations	PL-used	Encapsulated materials	Applications	Ref.
5.	Positively charged PC-based liposomes	Soybean phosphatidylcholine mixed with Gemini surfactants	Rhodamine B, DOX, Pralidoxime chloride	Penetrate the BBB and reactivate acetylcholinesterase	[86]
6.	Drug-in-cyclodextrin-in liposomes	DPPC, DMPC, DSPE-PEG_{2000}	17β-estradiol (E2)	Pharmacologic tools	[87]
7.	Thermosensitive Nanogoldstar@mesoporous silica@liposmes	DPPC, DSPE-PEG_{2000}	DOX & docetaxel	Chemophotothermal therapy	[88]
8.	Thermosensitive liposomes	Phosphatidylglycerol	DOX	Treatment for muscle-invasive bladder cancer (MIBC)	[89]
9.	Ultradeformable liposomes	Soy phosphatidylcholine	Ammonium glycyrrhizinate	Anti-inflammatory agent	[90]
10	Aromatized liposomes	1-palmitoyl-2-hydroxy-*sn-glycero*-3-phosphocholine	Anesthetic tetrodotoxin	DDS	[91]
11.	D-α-tocopheryl PEG1000 succinate conjugated Nano pro-liposomes	Unsaturated phosphatidylcholine (soybean lecithin)	Myricetin	Improvement of bioavailability of myricetin	[92]
12.	Siloxane-phosphocholine liposomes	DPPC, DPhyPC, POPC	Calcein	DDS	[93]
13.	Photosensitizer-doped plasma membrane-responsive liposomes	Hydrogenated soy phosphatidylcholine (HSPC)	DOX & protoporphyrin IX	Nuclear drug delivery	[94]
14.	Red blood cell-liposomes	DPPC & DOPE	Paclitaxel	DDS	[95]
15.	Liposomes with drug absorption enhancers	DOPC, DSPC, DPPC	Efavirenz & mefloquine	Anti-HIV and antimalaria	[96]
16.	Magnetoplasmonic elastic liposomes	DPPC	Calcium/magnesium ferrite nanoparticles with gold nanorods	Photothermal therapy	[97]
17.	Biomimetic hybrid magnetoliposomes	Soy phosphatidylcholine	Manganese ferrite Y IR780	MRI-guided thermal therapy	[98]
18.	Liposome-embedded nanofibers	Stearyl amine, soya lecithin	Irinotecan	Anticancer therapy	[99]
19.	Triphenylphosphonium-functionalized liposomes	PCDA/ DMPC	DOX	Mitochondria-targeted anticancer therapy	[100]

Engineered liposomes

In drug delivery, incorporating saturated phospholipids and cholesterol into liposome delivery systems does not fully resolve the issue of their interaction with serum components, which reduces the uptake of these vesicles by the mononuclear phagocytic system (MPS) [101]. Pre-saturating the MPS with bare liposomes may help address this problem. Additionally, SUVs have a limited aqueous entrapment volume, while the use of charged liposomes can raise concerns about toxicity. Various strategies have been developed to coat the liposome surface with inert molecules, creating a protective spatial barrier [102]. One approach under investigation involves crafting liposomes that mimic the composition of erythrocyte membranes. In this case, the liposome surface is modified by incorporating gangliosides and sialic acid derivatives, such as monosialoganglioside. Hydrophilic polymers are then applied to the liposome surface to enhance their hydrophilicity. The core idea is to use a hydrophilic polymer or glycolipid, like PEG or monosialoganglioside, with a flexible chain that occupies the area around the liposome surface, forming what is known as a periliposomal layer. This prevents MPS macrophages from interacting with liposomes if blood plasma opsonins cannot access and bind to their surfaces [103, 104]. By reducing MPS uptake, long-circulating liposomes can passively accumulate in various tissues or organs.

PEG is a widely explored polymer used to create stealth liposomes, enhancing their longevity in the bloodstream. It acts as an effective steric stabilizer, allowing liposomes to remain undetected in the circulatory system. One common approach involves incorporating PEG into the liposomal membrane through a cross-linked lipid, specifically PEG-distearoylphosphatidyl-ethanolamine [105]. PEG is biocompatible, soluble in both organic and aqueous environments, has minimal toxicity, and is non-immunogenic and non-antigenic, with favorable excretion properties. Liposomal surfaces can be modified with PEG in several ways, including physical adsorption, incorporation of PEG-lipid

conjugates during liposome preparation, or covalent attachment of reactive groups. Additionally, polymers like chitosan help shield the liposomal surface, particularly in the oral delivery of drugs, by creating a protective shell.

Synthetic routes of liposomes

The thin film hydration technique, commonly known as the Bangham method, is the first documented approach in liposome technology (Figure 3). An organic solvent, such as chloroform, ether, or methanol, is typically used to dissolve the lipids in this straightforward procedure [106]. The thin lipid film is then rehydrated with an aqueous solvent, leading to the formation of liposomes. GUVs are formed by a gentler hydration method, while MLVs are formed by intense agitation during hydration [107]. The reverse phase evaporation process is another method used to prepare liposomes. Phospholipid films are initially created by dissolving phospholipids in an organic solvent, and evaporation is used to desolvate the films [108]. The lipid film is typically reconstituted using additional organic solvents, commonly diethyl ether or isopropyl ether. An oil-in-water emulsion is then formed by introducing an aqueous phase. To achieve a uniform mixture, the emulsion is subjected to sonication, resulting in the formation of inverted micelles and a homogeneous emulsion. In the final step, the organic solvent is evaporated under reduced pressure, producing a thick gel containing liposomes suspended within it [109].

Solvent injection is another technique for preparing liposomes. This method involves the rapid injection of lipids, dissolved in an organic solvent such as ethanol or ether, into an aqueous solution, leading to the formation of liposomes [110]. While this technique has its advantages, it also faces several challenges, including limited lipid solubility in ethanol, inconsistent liposome formation due to insufficient agitation, low encapsulation efficiency for hydrophilic compounds, and difficulty in completely removing the ethanol. Another established technique for liposome production is the detergent removal method [111]. In this method, a detergent is used at its critical micelle concentration to solubilize phospholipids. After detergent removal, typically achieved through column chromatography or dialysis, and in the presence of an appropriate aqueous medium, phospholipid molecules spontaneously self-assemble to form liposomes. The detergent removal method has some limitations, including the potential presence of contaminants or impurities in the final product, the risk of interactions between the detergent and the encapsulated substance, and the time-consuming nature of the process.

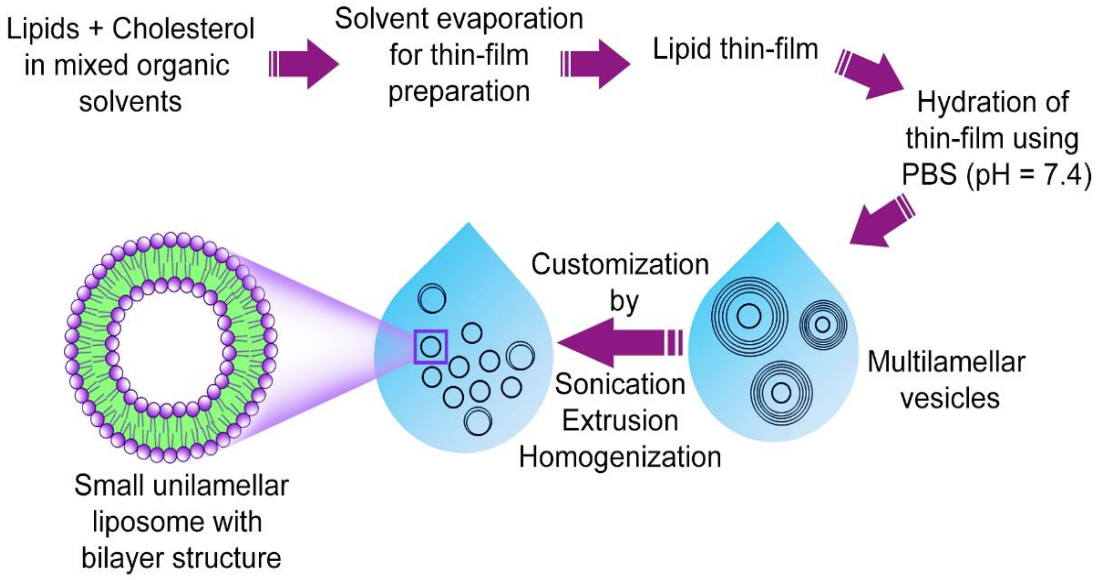

Fig. 3. Schematic representation of thin-film hydration technique to synthesize liposomes

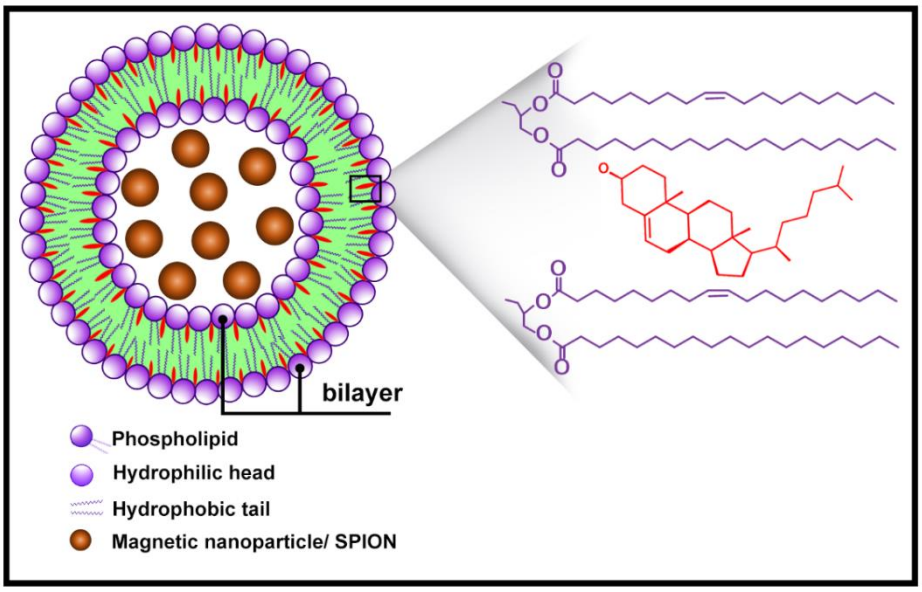

Fig. 4. Architectural fabrications of magnetoliposome shown in schematic diagram

Synthetic routes of magnetic liposomes

Lipid-based particles are engineered to create organized structures by utilizing their inherent self-assembling properties in aqueous environments. Liposomes typically form bilayer structures, although the specific structure can vary depending on lipid geometry and environmental conditions. Lipid composites can be formulated by incorporating SPIONs into the lipid structure, specifically in liposomes (Figure 4) [111]. These lipid nanocomposites become responsive to magnetic fields due to the presence of iron oxide nanoparticles. To form aqueous magnetoliposomes, synthetic magnetic nanoparticles are encapsulated in liposomes via sonication, where they are incorporated into the aqueous medium [112]. The way magnetic nanoparticles are associated with liposomes—whether they are entrapped in the aqueous core, embedded in the lamellar membrane, or adhered to the particle surface—requires distinct preparation techniques for each mode of association.

Approach to thin film hydration

The thin film hydration method is one of the most commonly used techniques for preparing lipid-based nanocomposites containing hydrophobic SPIONs. The process begins with dissolving precursor lipids in a volatile solvent, typically a mixture of methanol and chloroform, while simultaneously incorporating hydrophobic-coated SPIONs into the solution [113]. The solvent is then removed under vacuum conditions using a rotary evaporator, resulting in the formation of a thin lipid film on the inner surface of the container. Next, the lipid film, now containing the SPIONs, is fragmented and subjected to sonication above the transition temperature of the lipids, dispersing the mixture in excess water or buffer [114]. Through the extrusion process and further refinement, the multilamellar vesicles are converted into predominantly unilamellar vesicles, achieving the expected particle size and structure.

In a novel treatment for iron deficiency anemia, Fathy and colleagues created liposomes loaded with iron oxide magnetic nanoparticles using the thin film hydration method [115]. They added cholesterol and soybean phosphatidylcholine (1:2) in chloroform to obtain a thin film, then evaporated the solvent. The lipid film was hydrated by adding a solution of iron oxide magnetic nanoparticles, followed by sonication to entrap the nanoparticles within the liposomal structure. German et al. loaded hydrophilic magnetite fluid nanoparticles into liposomes, which were prepared using the thin film hydration technique, for use as an MRI contrast agent [116]. They dissolved a lipid-thin film made of egg phosphatidylcholine and phosphatidylinositol in a buffer containing magnetite hydrosol. Korolev et al. reported targeted delivery and theranostics using magnetic liposomes containing indocyanine green [117]. In 15 mL of chloroform, 75 mg of soy lecithin was dissolved, followed by 10 mL of vitamin E. Rotary evaporation was used to remove the organic solvent. To hydrate the dry film, an aqueous suspension of iron oxide nanoparticles was added to 0.9% NaCl and indocyanine green at a concentration of 1 mg/mL. Zhao et al. recently reported the use of glucose transporter-1-

mediated magnetic liposomes to treat bone metastatic breast cancer [118]. Novel glucose derivatives were synthesized as ligands for the development of magnetic liposomes, aiming to improve paclitaxel delivery to bone metastatic lesions. The paclitaxel-filled magnetic liposomes were synthesized using a thin film hydration technique with soybean phospholipids and Fe_3O_4 magnetic nanoparticles.

Approaches based on reverse phase evaporation (RPE)

RPE is another commonly used method to fabricate magnetoliposomes or other magnetically sensitive nanocomposites. This process involves dissolving lipids and iron oxide nanoparticles in a volatile solvent, such as chloroform, methanol, or diethyl ether, and then emulsifying the mixture with a surfactant solution. As the volatile solvent evaporates within the water phase, magnetoliposomes are formed. The RPE approach is ideal for formulations containing heat-sensitive components, such as biomolecules like proteins and enzymes, as it does not require high energy input, such as elevated temperatures or intense mechanical shear forces, as in thin film hydration. Additionally, the RPE approach encapsulates hydrophilic IONPs more efficiently in magnetoliposomes compared to conventional methods. Garcia-Jimeno et al. reported using an RPE process followed by a sequential extrusion procedure to obtain liposomes with a diameter of 200 nm, encapsulating anionic ferrofluid [119]. The study examined the efficiency of iron encapsulation across a range of iron/phospholipid ratios, from 0.016 mg iron per mM phospholipids to 0.024 mg iron per mM phospholipids, based on the initial magnetite concentration. This method achieved significantly improved encapsulation efficiency compared to extrusion alone for magnetoliposomes. In mice with induced inflammation and healthy mice, magnetic particles were administered intravenously. One hour after administration, iron levels were assessed in the exudates, livers, spleens, and plasmas of both groups. Exudates collected from inflammatory sites showed the accumulation of magnetoliposomes, indicating their potential for use in drug delivery for inflammation treatment.

Using alternating current and magnetic fields to control drug release, Brollo et al. developed magnetoliposomes in a single step [120]. They devised a simple, reproducible one-step approach to produce doxorubicin-loaded magnetoliposomes using the thin-layer evaporation method, generating liposomes approximately 200 nm in size composed of DPPC and IONPs. IONPs were integrated externally, internally, or within the lipid bilayers of these liposomes, with surface modifications that were negative, positive, and hydrophobic. An alternating magnetic field can effectively mitigate or eliminate side effects associated with these drug-loaded magnetoliposomes, which can release drugs precisely at specific locations and times. Zheng and colleagues developed thermosensitive magnetoliposomes as a novel carrier for targeted delivery and triggered release of coix seed oil [121]. Using a straightforward coprecipitation method, they synthesized polyethylene glycol-modified Fe_3O_4 nanoparticles, which were incorporated into thermosensitive materials or liposomes prepared by RPE techniques along with coix seed oil. Exposure to hyperthermia triggered rapid drug release and enhanced magnetic targeting, demonstrating their potential for cancer treatment.

Approaches rely on the double-emulsion principle

Double emulsions, recognized as emulsions of emulsions, represent liquid dispersion systems. In this process, a droplet of an emulsion, microemulsion, or liposome-like colloidal mixture is further dispersed in another dispersant, such as water or oil. The result is the formation of double-layered liquid droplets. These structures consist of an inner phase protected by emulsifiers or stabilizers, further dispersed and enveloped by an outer phase of emulsifiers [122]. Depending on the composition of the inner phase, these liquid-dispersed systems are commonly referred to as either water-in-oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O) double emulsions. A two-step emulsification process is employed to create both double emulsions and liposomes-in-double emulsion. The double emulsion method typically involves the formation of either O/W/O or W/O/W systems, which are then subjected to dehydration, solvent evaporation, and rehydration to produce magnetoliposomes. Pradhan and colleagues described the creation of magnetoliposomes using the double-emulsion method [123]. In this procedure, the initial emulsion, composed of water-in-oil (W/O), resulted from the combination of lipids and an aqueous dispersion of manganese ferrite. Additional water was then introduced into the system to generate a secondary emulsion in the form of W/O/W.

Rodrigues et al. reported nanocarriers for antitumor drugs based on magnetoliposomes made from manganese ferrite nanoparticles [124].

Manganese ferrite nanoparticles, with a size distribution of 26 nm, were successfully synthesized using the coprecipitation method. These nanoparticles exhibit superparamagnetism at room temperature and were subsequently entrapped in liposomes using the double-emulsion method. Initially, a dispersion was prepared by combining 10 µL of the synthesized $MnFe_2O_4$ nanoparticles with 3 mL of water, followed by centrifugation [124]. The particles deposited after centrifugation were resuspended in 10 µL of water using an ultrasonic homogenizer for 1 minute. To this aqueous dispersion, 3 mL of chloroform was added. After thorough agitation, 165 µL of 20 mM DOPG solution was introduced with vortexing to establish the initial lipid layer of the SMLs. The particles underwent two rounds of washing via magnetic decantation with pure water to eliminate any lipids not bound to the nanoparticles. The formation of the second lipid layer involved injecting 165 µL of 20 mM DOPG into the 3 mL aqueous dispersion of particles with the initial lipid layer while vortexing. The resultant solid magnetoliposomes underwent purification by centrifugation with pure water. Salvatore et al. investigated a drug delivery system comprising liposomes as a biocompatible lipid framework capable of accommodating both hydrophobic and hydrophilic drugs, along with a double-stranded DNA conjugated to a cholesteryl unit, which spontaneously incorporates into the lipid membrane. Further, SPIONs with hydrophobic and hydrophilic properties are either embedded within the lipid membrane of liposomes or linked to the DNA, respectively. Oleic acid-coated SPIONs were entrapped in DPPC liposomes using the double-emulsion method to form magnetoliposomes, creating a multifunctional drug delivery vehicle.

Gel-hydration method

A gel hydration technique was used by Nitica et al. to prepare thermosensitive magnetoliposomes loaded with doxorubicin [125]. They mixed 30 mg of DPPC, 15 mg of DSPC, and 5 mg of cholesterol to create a lipid mixture. To this lipid solution, 1.5 mL of a dispersion of Zn-ferrite nanoparticles in 1M aqueous ammonium sulfate solution was added. The resulting mixture was sonicated for 6 minutes, forming a microemulsion, which was then transferred to a rotary evaporator and maintained at a rotation speed of 220 rpm at 45°C. The resulting gel was subsequently hydrated with 18.5 mL of an aqueous solution of DOX at the required concentrations and vortexed to yield thermoresponsive magnetoliposomes loaded with the anticancer drug DOX. Cheung et al. developed unique SPION-embedded thermoresponsive liposomes made of lysolipid [126]. A lipid mixture was formulated by combining DPPC, MSPC, and DSPE-PEG2000, followed by the addition of N-palmitoyl-6-nitrodopamine-functionalized SPIONs. The lipid mixture was injected into a warm $(NH_4)_2SO_4$ solution to form a viscous gel-like substance. The generated liposomes underwent annealing for 1.5 hours at 60°C and were purified to yield lysolipid-containing heat-sensitive liposomes with a high DOX loading capacity.

Microfluidic-based synthetic approach

The versatility of microfluidics enables the manipulation of liquid flows within channels with diameters ranging from hundreds of micrometers to several millimeters. With a high-throughput experimental platform, rapid and adjustable mixing, and homogeneous reaction environments, this technology offers an appealing solution for a range of chemical synthesis and biological analysis applications [127]. Microfluidics has been used to modify particle size and improve size distributions by precisely controlling flow and mixing conditions. The controlled formation of liposomes has also been achieved using the well-established microfluidic hydrodynamic focusing method. Microfluidic systems have enhanced control over the physical properties of liposomes, resulting in magnetoliposomes with uniform size distributions, high loading efficiency, and reduced costs. There is growing interest in incorporating magnetic gradients in microfluidics separation methods to retain surplus magnetic nanoparticles while preserving the integrity of magnetoliposomes. The appeal of this approach lies in its versatility, applicability, and straightforward implementation, making it relevant for various biomedical applications such as disease diagnostics, therapeutics, and cell sorting.

Torres et al. demonstrated an economical microfluidic method for synthesizing and purifying magnetoliposomes [128]. An extensive biocompatibility and functional assessment was conducted, including tests for hemolysis, platelet aggregation, cytocompatibility, cellular internalization, and endosome escape. These evaluations aimed to determine the suitability of magnetoliposomes for gastrointestinal delivery. For synthesis, the microfluidic channels were purged with a 10 mL syringe containing 96% (v/v) ethanol for 15 minutes. An infusion pump was then used to connect a syringe filled with the lipid-nanoconjugate phase to another syringe containing

a 0.05 M NaCl solution. The syringes were attached to the microsystem using two probes. The synthesis process involved manipulating the total flow ratio, specifically at 2.5 mL/min and 5 mL/min [129]. A dynamic approach was also employed, varying the flow rate ratio from 1:1 to 5:1, representing different aqueous to solvent component ratios. This variation allowed for the exploration and optimization of synthesis conditions, providing a comprehensive study of how these parameters affected the process outcome. Moreover, the total flow rates, flow rate ratios, and magnetic nanoparticle concentrations were adjusted to achieve encapsulation efficiencies ranging from 20% to 90% [128]. Hemocompatibility, platelet aggregation, and cytocompatibility tests demonstrated remarkable biocompatibility of the magnetoliposomes. Additionally, the delivery outcomes were promising, showing significant internalization and minimal entrapment in endosomes. There were also negligible instances of nuclear damage and DNA condensation, further supporting the positive results. In conclusion, microfluidic device-based synthesis can efficiently encapsulate and deliver nanostructured cell-penetrating agents through high-throughput production of magnetoliposomes.

Classifications of magnetoliposomes

Magnetoliposomes can be classified into four main categories based on the arrangement of nanoparticles within the liposome structure (Figure 5). Solid-magnetoliposomes are composed of a single magnetic particle or a cluster of magnetic particles encased in a lipid bilayer membrane. Aqueous-magnetoliposomes contain magnetic nanoparticles dispersed in their inner aqueous lumen. Surface-conjugated magnetoliposomes consist of nanoparticles directly bonded to the surface of the liposome. Membrane-embedded magnetoliposomes have nanoparticles embedded within the lipid bilayer membrane. Additionally, plasmonic magnetoliposomes combine both magnetic and photothermal techniques. These systems can be manufactured by either encapsulating magnetic and plasmonic nanoparticles in aqueous magnetoliposomes or by incorporating them into separate compartments within liposomes.

Rodrigues et al. synthesized aqueous-magnetoliposomes using egg-yolk phosphatidylcholine [130]. In the ethanolic injection method, a 10 mM solution of egg-yolk phosphatidylcholine in ethanol was injected into an aqueous nanoparticle solution under vigorous vortexing. To eliminate non-encapsulated nanoparticles from the ferrofluid, water washing, magnetic decantation, and repeated centrifugation were performed after encapsulation. Solid-magnetoliposomes were formulated using DPPC and DOPG, resulting in a dual lipid layer surrounding the magnetite nanoparticles. Initially, 760 µL of the synthesized magnetic nanoparticles underwent centrifugation. The settled particles were then resuspended in 10 µL of water using an ultrasonicator operating at 189 W for one minute. To the aqueous nanoparticle dispersion, 3 mL of chloroform was added. After vigorous agitation, 165 µL of a 20 mM DPPC/DOPG solution was introduced under vortexing to form the initial lipid layer of the solid-magnetoliposomes [130]. Using a magnet, the particles were allowed to sediment, followed by a washing step to remove unbound lipids. The second lipid layer was created by injecting 165 µL of the same lipid solution into a 3 mL aqueous dispersion containing the particles with the first lipid layer, followed by vortexing. The magnetoliposomes were purified by centrifugation with pure water, then redispersed in 3 mL.

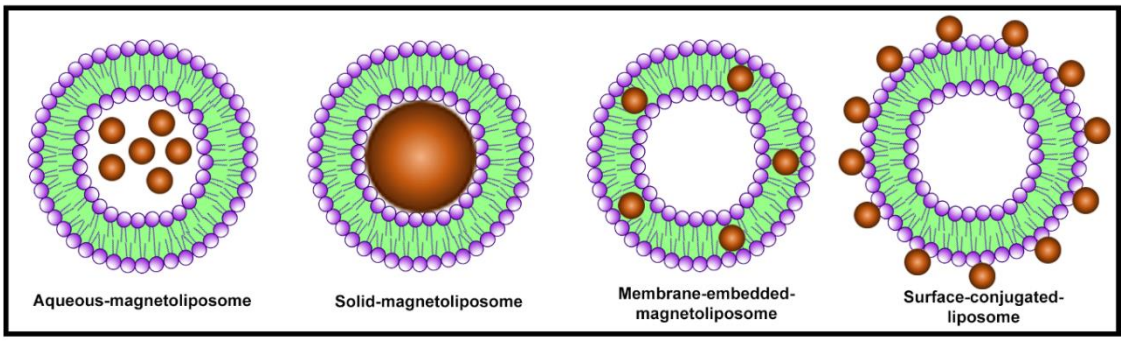

Fig. 5. Schematic representation to show the fabrications of aqueous-magnetoliposomes, solid-magnetoliposomes, membrane-embedded-magnetoliposomes and surface-conjugated-magnetoliposomes.

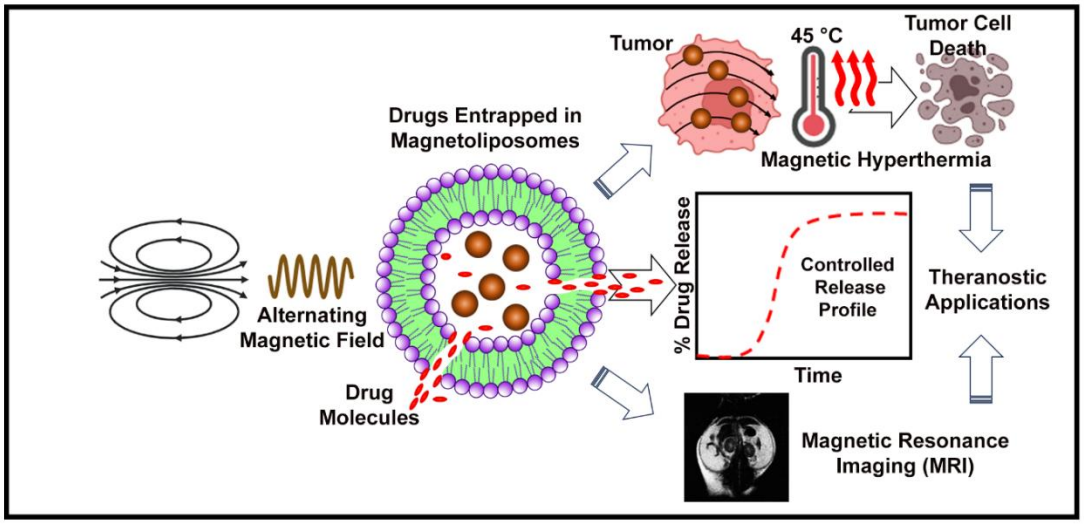

Fig. 6. Schematic representation of theranostic applications of magnetoliposomes that include the controlled release of drugs & magnetic hyperthermia-based therapeutic applications along with MR-imaging-based diagnosis.

Although not extensively investigated, magnetoliposomes with surface conjugation have been developed. In one study, Floris et al. examined how cationic nanoparticles interact electrostatically with anionic phospholipids, leading to the self-assembly of liposomes with magnetic nanoparticles on their surfaces [131, 132]. Hasa et al. reported another method involving electrostatic self-assembly, which combined anionic liposomes, magnetic iron oxide nanoparticles, and a cationic polyelectrolyte (poly-L-lysine) [133]. This combination resulted in the formation of sub-micrometer aggregates. Salvatore et al. documented an alternative method that avoids relying on electrostatic interactions [134]. In this approach, cholesteryl units conjugated with double-stranded DNA were attached to magnetic nanoparticles, facilitating the attachment of nanoparticles to the outer leaflets of the bilayer and their spontaneous anchorage.

Biomedical applications of magnetoliposomes

Magnetoliposomes as a drug delivery vehicle

The integration of drugs into nanoparticles can enhance traditional chemotherapy by improving stability and solubility, reducing systemic clearance, and increasing the specificity of the drug. In addition to effectively encapsulating both hydrophilic and hydrophobic drugs, lipid formulations can be modified with a variety of targeting ligands, such as proteins, peptides, nucleic acids, and small molecules, to achieve high therapeutic efficacy [135]. Controlling the release of drugs from conventional liposomes is often challenging due to slow and uncontrolled release. To address this, optimizing targeting and timed release is essential, as not all tumors share the same vascular characteristics. To improve drug delivery efficiency, minimize side effects, and enable effective treatment, magnetoliposomes—liposomes combined with magnetic nanoparticles—were developed. By using a magnetic field gradient, magnetic nanoparticles can be incorporated into liposomes, allowing for precise manipulation and control at the nanoscale. This manipulation encompasses signal conduction, magnetic targeting (primarily when the system exhibits a robust magnetic moment), and both passive and active targeting strategies. Additionally, alternating magnetic fields can trigger the release of drugs as an external stimulus [136]. This approach complements the exploration of endogenous stimuli and the application of magnetic hyperthermia as adjuvant therapy (Figure 6). Notably, magnetoliposomes function as theranostic agents, enabling both diagnosis and therapy. Magnetic resonance imaging benefits from the T2 shortening effect induced by magnetic nanoparticles, allowing for effective monitoring.

A streamlined approach to expedite drug release from lipid vesicles involves incorporating magnetic nanoparticles, either within the membrane or in the aqueous core. Release is activated upon exposure to an alternating magnetic field [137]. In magnetoliposomes, these embedded magnetic nanoparticles also facilitate the targeted delivery and accumulation of the loaded drug at specific sites through a magnetic gradient. The drug is then released by applying the alternating magnetic field. Typically, a high-frequency

alternating magnetic field ranging from 50 to 400 kHz is used to induce local heating of magnetic nanoparticles, a process known as hyperthermia. This elevated temperature near the nanoparticles causes thermal ablation of nearby cells, offering a targeted treatment with minimal damage to healthy tissues. Recent advancements have demonstrated that a low-frequency alternating magnetic field, within the range of 0.01 to 10 kHz, can also effectively promote the release of drugs from magnetic nanocomposites. This safer, low-frequency approach expands the potential applications of magnetic nanocomposites in drug delivery, offering greater versatility and minimizing the risks associated with high-frequency methods. Nappini and colleagues explored the effect of a low-frequency alternating magnetic field on the permeability of magnetoliposomes [138]. In their investigation, they examined both hydrophilic and hydrophobic cobalt ferrite ($CoFe_2O_4$) nanoparticles loaded in the aqueous core and lipid bilayer, respectively. The aim was to understand how the application of a low-frequency alternating magnetic field influences the permeability of magnetoliposomes containing these distinct types of nanoparticles in different locations within the liposomal structure. Research on hydrophobic cobalt ferrite nanoparticles coated with oleic acid suggests that the mechanism of slow release involves the formation of local pores or defects at the membrane level [138]. In contrast, fast release is associated with increased membrane permeability, which may result from structural changes in the lipid bilayer. These findings suggest that the nature of the release, whether slow or rapid, is closely linked to specific membrane-level changes, offering valuable insights into the controlled release dynamics of hydrophobic cobalt ferrite nanoparticles in lipid-based systems. Conversely, vesicles containing citrate-coated cobalt ferrite nanoparticles exhibit a different mechanism, involving the formation of pores in the lipid bilayer. This phenomenon is attributed to both hyperthermic effects and the oscillation of nanoparticles within the vesicle pool at the applied frequency [139]. The observed behavior of these magnetic vesicles under the influence of a low-frequency alternating magnetic field positions this system as a promising candidate for controlled drug delivery. Several other applications are summarized in Table 2.

Table 2. Applications of magnetoliposomes in drug delivery

No.	Magnetic nanoparticles	Liposomes used	Drug loaded	Applications	Ref.
1.	Fe_3O_4	Thermosensitive liposomes were synthesized by reverse-phase evaporation using DPPC & Cholesterol (4:1)	Dox	Diagnosis & synergistic treatment for cancer	[140]
2.	Ultrafine 50 nm sized magnetite	Reverse evaporation using soybean phosphatidylcholine, cholesterol, disetylphosphate & tocopherol	Paclitaxel	Breast cancer therapy	[141]
3.	Fe_3O_4	Thin-film hydration using DPPC & DSPE-PEG2000	Protoporphyrin IX	PDT-based cancer treatment	[142]
4.	Magnetosome protein MamC-mediated biomimetic magnetic nanoparticles	Thin-film hydration using DSPC	Dox	Drug carrier for cancer therapy	[143]
5.	Iron oxide nanoparticles	Thin-film hydration using DPPC/DSPE-PEG2000/Cholesterol (12:1:8)	Dox	Ultrasound-based combinatorial cancer therapy	[144]
6.	SPION	Thin-film hydration using DPPC/DSPE-PEG2000/Cholesterol	Dox	Magnetic hyperthermia for cancer treatment and MRI contrasting	[145]
7.	Magnetite nanoparticles	Thin film hydration technique using DPPC/cholesterol (10:1)	Gemcitabine & paclitaxel	Magnetic hyperthermia and controlled release of drugs	[146]
8.	$Ca_{0.25}Mg_{0.75}Fe_2O_4$ (Calcium substituted magnesium ferrite)	DPPC/Cholesterol & DPPC/ DSPE-PEG	Dox	Magnetic hyperthermia & pH-responsive drug release	[147]
9.	$CaFe_2O_4$ (calcium ferrite)	Ethanol injection method using egg L-α-phosphatidylcholine/ DPPC	Derivatives of Thieno(3,2-b)pyridine	Combined breast cancer therapy	[148]
10.	Core-shell nickel ferrite @ gold nanoparticles	Solid magnetoliposomes of DOPG & rhodamine B doped DOPE	-	Thermotherapy	[149]
11.	Flower-shaped multicore manganese ferrite	DPPC	Thienopyridine	Chemotherapy & thermotherapy	[150]

No.	Magnetic nanoparticles	Liposomes used	Drug loaded	Applications	Ref.
12.	Dimercaptosuccinic acid conjugated $Ca_{0.25}Mg_{0.75}Fe_2O_4$	DPPC/DSPC/cholesteryl hemisuccinate	Dox	Controlled release of anticancer drugs	[151]
13.	Manganese ferrite @ gold plasmonic nanoparticles	Ethanolic injection using egg phosphatidyl choline/ DPPC	Bovine lactoferrin	Stimuli-responsive antifungal therapy	[152]
14.	$MnFe_2O_4$	Lipid film hydration & co-extrusion using soy phosphatidyl choline & cholesterol	Dox	Targeted anticancer therapy	[153]
15	$MgFe_2O_4$	Solid magnetoliposomes of Egg-phosphatidylcholine/DPPC/DSPE-PEG2000	Curcumin	Magnetic hyperthermia with chemotherapy	[154]

Role in medical imaging

MRI often lacks sensitivity, so the use of contrast agents, such as paramagnetic Gd^{3+} or SPIONs, is a common strategy to improve detection limits and enhance the visualization of specific organs or cells. However, the widespread use of Gd^{3+} is limited by its toxicity, requiring the use of chelates and an efficient renal clearance process for contrast agents. Unfortunately, achieving efficient renal clearance remains a challenge. To address this, SPIONs are frequently used as alternative contrast agents. However, careful attention must be given to the surface modification of the metal oxide cores to prevent significant aggregation, which could compromise their suitability for various in vivo applications. Numerous coating materials have been developed for this purpose, including dextran, polymers, silica, noble metal nanoparticles, and lipids, which encapsulate SPIONs in magnetoliposomes. This variety of coating materials allows for the customization of SPION surfaces, ensuring their stability and functionality in diverse biomedical contexts. The integration of magnetic nanoparticles with liposomes to form magnetoliposomes demonstrates their versatility in various applications. Through this integration, PEG can be added to extend the liposomes' circulation time in the bloodstream. Additionally, attaching biomolecules, peptides, or antibodies to the liposomes enhances their effectiveness by facilitating targeted delivery to specific sites. These magnetically enhanced liposomes can also be used in conjunction with other imaging techniques, such as optical imaging or tomography, to synergistically harness their magnetic properties. Furthermore, their ability to incorporate anticancer drugs provides a multifaceted approach to therapeutic interventions.

The magnetoliposome class of MRI contrast agents has been highlighted by numerous researchers [155, 156]. By incorporating hydrophilic iron oxide nanoparticles into a liposome's aqueous core, the particles are less likely to aggregate under physiological conditions, leading to enhanced tissue accumulation and improved imaging [157]. Conversely, integrating hydrophobic iron oxide nanoparticles into the lipid bilayer of liposomes has shown superior MRI imaging capabilities compared to free iron oxide nanoparticles [158]. This breakthrough has advanced the development of magnetoliposomes as T2 contrast agents. However, further research is needed to assess the impact of lipid bilayer composition on the MRI properties of magnetoliposomes. The relaxivity of any contrast agent, whether longitudinal (r_1) or transverse (r_2), is defined by the ratio of the water relaxation rate constant to its concentration [159]. High relaxivities offer significant benefits, as they can provide equivalent contrast effects at lower doses, thereby reducing systemic toxicity while maintaining effective contrast. Nanoparticle surface coatings and magnetization affect how water molecules relax near magnetic centers. The surface coating can significantly influence water molecule relaxation through diffusion, retention, hydration, and hydrogen bonding [160]. By modifying the accessibility of water protons to magnetic centers, the fluidity of the lipid bilayer—a crucial component of magnetoliposomes—significantly impacts relaxivity values. Several factors, including the length and saturation of phospholipid hydrocarbons and cholesterol content, determine this fluidity. Studies involving Gd-chelates with liposomes and liposomes encapsulated with iron oxides have shown that these factors influence MRI signals.

Bolte and colleagues demonstrated that magnetoliposomes are formed when magnetite nanoparticles are embedded within large unilamellar vesicles coated with dextran [161]. These magnetoliposomes were not only effective for labeling human blood mononuclear cells but also for labeling peripheral blood lymphocytes and monocytes. Labeling efficiency was significantly enhanced, as reflected by a threefold increase in r_2 compared to dextran-coated magnetite

nanoparticles functionalized with monoclonal antibodies. Compared to other nanoparticle-based cellular labeling methods, magnetoliposomes offer distinct advantages. Kostevsek and collaborators conducted an extensive study on the impact of various phospholipids on the r_2 values of magnetoliposomes containing magnetic nanoparticles within the bilayer [155]. Their analysis revealed a strong correlation between bilayer fluidity and r_2, highlighting the critical role of lipid composition in influencing relaxivity. Incorporating 5 nm iron oxide nanoparticles into the lipid bilayer resulted in a remarkable enhancement in relaxivity. Specifically, r_2 values increased substantially, from 153 s^{-1} mM^{-1} for DPPC/cholesterol/DSPE-PEG to 673 s^{-1} mM^{-1} for DOPC/DSPE-PEG. This improvement was striking compared to free iron oxide nanoparticles, which had an r_2 value of 16 s^{-1} mM^{-1}, as measured on a 9.4 T MRI scanner. This finding underscores the potential for tailoring magnetoliposome formulations to optimize relaxivity for magnetic resonance imaging applications. Grappin et al. developed a multifunctional approach by designing RNA-loaded magnetoliposomes [162]. RNA-loaded liposomes serve as potent antitumor immune stimulators and early biomarkers of treatment response. Compared to electroporation, these particles are more effective at activating dendritic cells and inhibiting tumor growth. By incorporating iron oxide, dendritic cells can be transfected more efficiently, and their migration can be monitored using MRI. The antitumor response is predicted by T2-weighted MRI intensity in lymph nodes, which is strongly correlated with dendritic cell trafficking. In preclinical tumor models, individuals identified as responders via MRI just 2 days after vaccination showed significantly reduced tumors 2 to 5 weeks post-treatment and lived approximately 73% longer compared to nonresponders [162]. Based on these findings, this straightforward and scalable nanoparticle formulation not only generates robust anticancer immune responses but also predicts individual treatment outcomes using MRI. Further research findings are provided in Table 3.

Table 3. Applications of magnetoliposomes in medical imaging

Sl. No.	Magnetoliposomes used	Methods for magnetic fraction fabrication	Methods for liposomal formulations	Imaging applications	Ref.
1.	Liposomal polyethylenimine (PEI)-coated SPION	Coprecipitation for SPION synthesis & thiourea reaction for PEI coating	Ethanol injection	MRI-based diagnosis & gene therapy	[163]
2.	PEI-coated SPION loaded in lipid polycationic-gene vector-loaded liposomes with a positive charge.	Coprecipitation for SPION & thiourea reaction for PEI coating	Ethanol injection	Gene therapy and MRI-based theranostic applications in liver cancer	[164]
3.	DSPC magnetoliposomes with charge-stabilized magnetic iron oxide nanoparticles	Coprecipitation followed by peptization	Thin film hydration	Improved magnetic particle imaging (MPI)	[165]
4.	Vitamin-E functionalized $MnFe_2O_4$ encapsulated in nanoemulsions made of sphingomyelin	Chemical thermodecompositio n	Ethanol injection	Improved biocompatibility & in vivo and ex vivo MRI contrasting	[166]
5.	Gold-decorated $MnFe_2O_4$ magnetoliposomes (DPPC) loaded with thienopyridine	Coprecipitation and seeding method	Thin film hydration	Cancer theranostics, including chemotherapy and photothermia	[167]
6.	SPION-based magnetoliposomes linked to anti-LIBS	Procured	Dual asymmetric centrifuge	MRI contrasting-based activated platelets targeting	[168]
7.	Ultra small SPION coated by citrate/dextran/PEG5000 entrapped in liposomes made of DPPC/Cholesterol/DSPE-PEG2000/malemide-PEG2000-DSPE	Procured	Film rehydration	High ratio of r2/r1 MRI contrast targeting anti-Her2 & Herceptin	[169]
8.	Iron oxide nanoparticles loaded in liposomes of soybean phosphatidylcholine (SPC) /cholesterol	Coprecipitation	Film followed by extrusion	T2 MRI contrast agent	[170]
9.	Ultrasmall SPION loaded in thermoresponsive liposomes made of DPPC/SPC/cholesterol/DSPE-PEG2000.	Coprecipitation	Lipid film rehydration	MRI-driven HIFU (high-intensity focused ultrasound) for local hyperthermia, controlled drug release, and imaging.	[171]
10.	Vesicles made of phosphatidylethanolamine conjugated diethylene triamine pentaacetic acid holding Gd^{3+}	Gd-DTPA	Thin film hydration and sonication	Biocompatible contrast in dynamic MRI	[172]

Smart magnetoliposomes for theranostic applications

These smart magnetoliposomes can be activated to release various drugs in response to specific physiological conditions. Triggers may include changes in pH, enzymatic activity, transition temperature, the application of magnetic fields to diseased tissues, light induction, or ultrasound [173-175]. Using external stimuli to trigger drug release ensures greater precision in timing and location, as well as better control over drug delivery and dosage. Wang et al. developed a dual-targeting delivery system using magnetic liposomes, incorporating mannose-modified magnetic nanoparticles on their surface [176]. This system is designed to respond to a static magnetic field and specifically target M2 macrophages via mannose receptor-dependent uptake. Various physical and chemical tests were used to characterize the nanoparticles, and in vivo imaging demonstrated their accumulation in damaged lung tissue. The treatment successfully decreased M2 macrophages and their polarization, slowing the progression of idiopathic pulmonary fibrosis by locally releasing dexamethasone in response to the static magnetic field. Additional research showed reduced α-smooth muscle actin expression and collagen buildup, highlighting the potential of this system as an effective therapy for pulmonary fibrosis. Poornima G. et al. developed a green method for synthesizing quercetin-encapsulated magnetoliposomes using Punica granatum L peel extract to stabilize Fe_3O_4 nanoparticles [177]. The resulting nanoformulations, approximately 100 nm in size, exhibited antioxidant properties and effectively reduced lipid peroxidation. They also demonstrated high heating efficiency (∼57 to 60 W/gFe) under safe magnetic exposure. In vitro experiments showed a 45% decrease in the viability of MG-63 osteosarcoma cells while causing minimal toxicity to non-cancerous HEK-293 cells, underscoring the potential of these magnetoliposomes for cancer theranostics. Rocha and colleagues synthesized cell-membrane-based hybrid nanoparticles to enhance drug delivery and cancer theranostics [178]. These biomimetic nanovesicles, which incorporate magnetic nanoparticles and IR780 dyes, utilize membranes derived from red blood cells, melanoma cells, and glioblastoma cells. The Mn-ferrite nanoparticles, with a core size of approximately 15 nm, exhibit high transverse relaxivity values. Both magnetic nanoparticle-based hyperthermia and photothermal therapy achieved therapeutic temperatures with approximately 28% efficiency. In vivo experiments demonstrated effective accumulation of the nanoparticles in tumors via intratumoral, intravenous, and intraperitoneal administration, suggesting their potential for multimodal cancer theranostics.

Nanohybrid liposomal-magnetic particle systems represent a promising advancement in drug delivery platforms for cancer theranostics. While current nanomedicines enhance tumor targeting and reduce side effects, several challenges must be addressed before they can be applied clinically [179]. Careful selection of hybrid components in liposomal vesicles and magnetic cores is crucial for preventing drug leakage, ensuring high entrapment and loading efficiency, and achieving favorable pharmacokinetic behavior. Additionally, these systems enable the co-delivery of chemotherapeutic drugs, which can effectively combat drug resistance in specific tumor cells. Theranostic nanohybrid structures enhance treatment efficacy through both targeted and non-targeted mechanisms, leading to improved overall treatment outcomes. Veloso et al. proposed a novel method to enhance therapeutic efficacy through the sequential co-delivery of drugs, specifically Dox and methotrexate, using a co-assembled hydrogel made from an RGD-functionalized dehydropeptide [180]. This gel incorporates magnetoliposomes and mesoporous silica-coated gold nanorods, allowing for independent regulation of drug release. The properties of these nanostructures are enhanced by the addition of liposomes or nanorods and their co-assembly with the RGD-functionalized peptide. The system supports orthogonal drug release activated by photothermia and magnetic hyperthermia, significantly improving its effectiveness against 3D cancer cell cultures. Additionally, the gel demonstrates favorable characteristics, including injectability, rapid gelation, self-healing abilities, and suitable mechanical properties for drug delivery, making it a promising multimodal platform for cancer therapy. Elbeltagi et al. focused on developing magnetoliposomes for breast cancer therapy by synthesizing nickel ferrite magnetic nanoparticles encapsulated within liposomes and loading them with quercetin to produce quercetin-magnetoliposomes [181]. The encapsulation of quercetin was highly efficient, achieving a drug loading of approximately 7.3% and an entrapment efficiency of about 83%. Magnetic hyperthermia treatment resulted in specific absorption rates of 200 W/g for the quercetin-magnetoliposomes. In vitro experiments demonstrated a 62% release of quercetin at pH 5.1 and 44% at physiological pH

after 24 hours. The cytotoxicity of quercetin-magnetoliposomes, free quercetin, and magnetoliposomes was assessed using the MCF-7 cell line, highlighting their potential for cancer theranostics. Magnetoliposomes are being studied for various biomedical applications due to their biocompatibility, hemocompatibility, biodegradability, negligible toxicity, and ability to be controlled by external stimuli, primarily magnetic fields and other factors. They are used in cancer hyperthermia, magneto-drug targeting, magnetofection, and MRI, serving both single and multi-purpose theranostic roles.

Magnetic hyperthermia-based theranostic applications

In magnetic hyperthermia, the temperature is raised locally or throughout the body to between 40 and 45 °C, exposing tumor tissues to the elevated temperature while sparing adjacent healthy tissues, which can tolerate it [182]. Tumor regions exhibit pathophysiological traits, including leaky vasculature and disorganized cellular architecture. These characteristics hinder the efficient dissipation of heat within cancerous tissues. The use of magnetic nanoparticles in an alternating magnetic field has been shown to effectively dissipate heat in tumor areas, addressing this challenge. When exposed to an alternating magnetic field, a ferrofluid containing SPIONs or other magnetic nanoparticles dissipates thermal energy once its magnetic energy exceeds its anisotropy energy [183]. Brownian motion and Néel relaxation processes are responsible for generating heat in magnetic nanoparticles through susceptibility losses, which are quantified by the specific absorption rate. Particle size and shape anisotropy play key roles in these processes. Magnetic hyperthermia treatment induces cellular distortion in the tumor microenvironment by accumulating biocompatible magnetic nanoparticles in tumor areas. Depending on factors such as cell type, nanoparticle location, and temperature, this distortion ultimately leads to the death of cancer cells through apoptosis or necrosis [184, 185]. Magnetic hyperthermia holds promise as a targeted and effective cancer treatment strategy due to the complex interplay of these factors.

To minimize systemic toxicity and facilitate prolonged circulation before clearance, magnetic nanoparticles must be designed with biocompatibility and bioavailability in mind [186]. The biocompatibility of magnetic nanoparticles, including SPIONs, can be enhanced using polymers or small molecules, such as citrate, in nanochemistry. An appealing approach is to encapsulate magnetic nanoparticles within or between lipid bilayers to create magnetoliposomes, offering a range of potential advantages. Lipid vesicles have a natural affinity for biological membranes, making them excellent delivery vehicles for both the vesicles and their cargo [187]. When preparing magnetoliposomes for magnetic hyperthermia, selecting the appropriate lipids is crucial for effective treatment. A key characteristic of thermosensitive liposomes is their ability to undergo a gel-to-liquid phase transition above a critical temperature. This property enables the controlled release of encapsulated payloads, including drugs, small molecules, or genetic materials, upon thermal activation. These liposomes also maintain their structure while enhancing the permeability of the lipid bilayer. Incorporating magnetic nanoparticles into liposomes not only improves their stealth properties but also extends their circulation time [188]. The combination of magnetic nanoparticle-based hyperthermia and chemotherapy in a controlled, synergistic manner makes these liposomes versatile drug delivery agents, with the added benefit of magnetic nanoparticles aiding in image-guided theranostic applications.

The work of Theodosiou et al. involved the engineering of iron oxide nanoflowers in two sizes, 15 and 35 nm, each coated with citrate or Rhodamine B [189]. The colloidally stable citrate-coated nanoflowers were encapsulated in thermosensitive liposomes through extrusion, followed by loading Rhodamine B into the lipid-based bilayer structures. All the nanoformulations demonstrated hemocompatibility and cytocompatibility. However, the 35 nm nanoflowers, even at lower concentrations than their 15 nm counterparts, proved to be more effective nanoheaters for magnetic hyperthermia. Following magnetic hyperthermia, Rhodamine B-loaded magnetoliposomes containing 35 nm nanoflowers exhibited promising therapeutic and imaging properties against lung adenocarcinoma. Guo et al. developed a PEGylated carboxymethyl-dextran-functionalized magnetoliposome loaded with Dox, making magnetoliposomes suitable for theranostic applications [190]. MRI was performed using biocompatible magnetoliposomes as T2-contrast agents, and doxorubicin (Dox) was released over a sustained period in response to low-frequency alternating magnetic fields. This serves as an excellent example of theranostic applications of magnetoliposomes.

CONCLUSION

Magnetoliposomes represent a promising nanosystem that combines magnetic nanoparticles with liposomes to provide a synergistic effect. Over the past decades, numerous research groups have focused on improving synthetic procedures and extensively exploring the applications of these nanosystems. Magnetoliposomes enable the creation of multimodal and multifunctional theranostic agents, allowing for the sustained, controlled, and sequential release of therapeutic substances. In addition to encapsulating a wide range of drugs, various architectural designs have been developed to enhance magnetic responsiveness, facilitate triggered drug release, and achieve other specific purposes. A variety of novel synthesis methods have been employed to improve nanostructure entrapment efficiency, ensure system homogeneity, and fabricate complex nanostructures. As imaging contrast agents and real-time diagnostic tools, magnetic nanoparticles play a crucial role in magnetoliposomes. Furthermore, by combining magnetic and plasmonic materials, novel imaging techniques have been explored, refining theranostic properties. In the field of nanomedicine, there has been a surge in research on magnetoliposomes to realize their full potential in advancing functional diagnostics and targeted drug delivery through these nanostructures.

Engineered magnetoliposomes for biomedical applications face several challenges, including the lack of comprehensive characterization of hybrid nanostructures, which hinders the development of nanocarriers. Thorough characterization requires the use of multiple interdependent and complex techniques. Magnetoliposomes are intricate structures that demand expertise from various fields, including chemistry, physics, biophysics, magnetism, engineering, pharmacology, and medicine, due to their complexity. A multidisciplinary approach is essential for understanding these nanostructures holistically. Continuous research is necessary to advance magnetoliposomes for biological applications, and the synthesis and characterization of magnetoliposomes must overcome several obstacles. Despite their clinical recognition, studies consistently identify opportunities to improve liposome efficacy. Researchers continue to discover novel approaches to surface functionalization and dynamically optimize cell uptake. To ensure safe thermal treatments, the properties of magnetic nanoparticles need to be enhanced, particularly to prevent harm to healthy cells. Furthermore, there is a pressing need to improve the magnetic characteristics of these nanostructures. A significant challenge remains in developing magnetic nanoparticles with a high specific absorption rate that can be effectively transported within the human body. Additionally, addressing the issue of increased penetration depth is crucial for advancing in vivo applications of magnetoliposomes. This field of hybrid nanostructures must be continuously investigated and innovated to fully unlock their potential.

ACKNOWLEDGMENTS

The authors express their gratitude to CARE for providing infrastructural support. PD, VK, AT, and KH sincerely thank CARE for offering research fellowships and financial assistance.

ETHICAL APPROVAL

This review article does not contain any studies performed by any author with human participants or animals.

FUNDING

This review article received no funds.

CONFLICTS OF INTEREST

The authors declare there are no competing interests to declare.

DATA AVAILABILITY

All the data have been included in the manuscript.

AUTHORS CONTRIBUTION

PD and KG gathered the data, analyzed it, and wrote the initial draft; DB, AT, KH, and VK contributed additional data and verified it. AG was responsible for the conception, design, further data collection, illustrations, analysis, and final preparation of the manuscript. All the authors have approved the final version.

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