Ultrasound-Responsive Materials for Drug/Gene Delivery

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Abstract–Due to its low risk, high accuracy, and deep penetration into tissue, Ultrasound (US) has become one of the most widely used methods in the diagnosis and treatment of disease. US is gaining more attention in the Drug/gene Delivery Systems (DDS) due to the countless benefits it offers in relations of site-precise delivery as well as spatial statementdelivery of medications/genetic factor. The most popular type of ultrasound-responsive delivery material is Microbubbles (MBs). Nanobubbles, droplets, micelles, as well as nanoliposomes are just some of the recent innovations in this area that serve as carriers. In order to encourage further research into ultrasound approachable materials as distributioncarters, we review recent successes with novel ultrasound receptive materials (Microbubbles (MBs), Micelles, Liposomes and Niosomes) and deliberate the challenges associated with using Ultrasound-Responsive Materials (US-RM) in Drug Delivery Systems (DDS).

Keywords – Drug Delivery Systems (DDS), Ultrasound (US), Ultrasound-Responsive Materials (US-RM), Microbubbles (MBs)

I. INTRODUCTION

In order to battle diseases, pharmaceuticals are crucial tools. Pharmaceuticals are often classified into two broad categories, hydrophilic and lipophilic, based on their solubility profiles. Since cell membranes are mostly made of lipid bilayers, hydrophilic medicines often have difficulty entering cells through passive diffusion. Lipophilic medications, on the other hand, may be challenging to dissolve in water and often have poor bioavailability. The treatment of diseases caused by mutant genes has recently shown promise thanks to the development of gene drugs such as Deoxyribonucleic acid (DNA) drugs and Ribonucleic acid (RNA) drugs. These gene medications are significantly bigger and have trouble penetrating cells, unlike chemical treatments. Meanwhile, nucleases in the blood or cells quickly break down gene therapies.

Drug distributioncarters are cast-off to summarise pharmaceuticals in order to overcome the inadequacies of chemical and gene therapeutics in clinical procedures by increasing aquatic solubility of lipotropic medications, increasing diffusion of hydrophilic treatmentshooked onlockups, and decreasing sideeffects. Curcumin (diferuloylmethane), a type of hydrophobic polyphenol, is more bioavailable and water-soluble after being encapsulated in nanoliposomes, and its anticancer activity is also increased. Furthermore, delivery systems can prevent extracellular and intracellular enzymes from degrading gene drugs, thereby improving therapeutic efficacy.

Dosage, spatial, and temporal control are all factors that must be taken into account while developing advanced drug delivery systems (DDS). Microspheres and nanoparticles have been found to enhance therapeutic results by shielding medications or genes from adverse effects in a number of separate investigations. However,main drawback of microspheres and nanoparticles is their uncontrolled release of medications and genetic factor at the illness site. Since 1978, researchers have looked into stimuli-responsive delivery systems as a way to control the announcement of drugs and genes at specific sites. In addition to external stimuli like photons, electromagnetic, and ultrasound waves, microenvironment pH and enzymes in boardcapitals have become increasingly popular in recent years. It offers a fresh

angle on the investigation of delivery systems for controlled drug and gene release. As a non-invasive, inexpensive, and easily transportable physical stimulus, ultrasound has great potential for use in drug and gene delivery.

Diseases are diagnosed and treated with ultrasound, which comes in both littleincidence (100 kHz) and bigamount (>100 kHz and MHz variety) forms. Increased porousness of bosses into living prisons has been shown to be a result of ultrasound since the mid-1990s. The thermal and non-thermal effects of ultrasound sonication are primarily responsible for the increased efficacy with which drugs/genes are transported. When acoustic energy is absorbed by biological tissues, heat is generated. Ultrasound weight, acoustic cyclosis, reactions, runny microjet, and ultrasound broughtswaying or cavitation are the primary sources of the non-thermal effects. In particular, ultrasound displays improved delivery efficiency when cavitation nuclei, particles that dampen acoustic intensity and induce cavitation, are present.

Due to the benefits of cavitation nuclei in ultrasonic stimulation, microbubbles have been extensively exploited in ultrasound-mediated drug/gene delivery. Microbubbles are often made up of a gaseous core surrounded by a shell made of phospholipids, polymers, or proteins. Because of their small size (between 1 and 10 m), microbubbles may travel through the bloodstream with RBCs. Microbubbles, which have been shown to respond to ultrasound, have been used in medication delivery studies. Controlling the delivery of cargo similarmedications and genetic factorresources with an ultrasonic change visualizing action has been confirmed by these scientifichearings. Notably, a large number of preclinical studies were also being evaluated. By combining doxorubicin-loaded microbubbles with ultrasound (1 MHz), Fu et al. [1]were able to significantly increase the drug's delivery by osteosarcoma cells, resulting in a 3.7-fold decrease in cancer development associated to doxrubicin-loaded microbubbles deprived of sonication. Growth blood flow and tissue volume were tracked using microbubbles containing doxorubicin. To speed up fracture recovery, Franco-Urquijo, Navarro-Becerra, Ríos, and Escalante [2]used an ultrasound microbubble delivery system to administer miR-29b-3p.

Microbubbles that respond to ultrasound can improve drug delivery even in difficult-to-reach tissue like articular cartilage. Unfortunately, due to their small size, microbubbles cannot cross the barrier between blood arteries and the tissues they are intended to treat, resulting in a limited blood circulation time. Tumor tissues, for example, only allow very small particles to enter (1 m). The EnhancedPenetrability and Retaining (EPR) effect in specificallow nanoparticles of size 1-100 nm to accumulatetop levels in tumormatters. The past developments in the field of nanotechnology have resulted in the development of novel nanomaterials for use in ultrasoundresponsive Drug-Delivery Systems (DDS), such as nanoscale foams, droplets, micelles, and nanoliposomes. Ultrasound has been used in trials to deliver drugs within liposomes. We'll go through some of the most important nanoscale ultrasoundresponsive resources for drug/gene distribution. The progress made and the difficulties encountered during the delivery of drugs and genes using US-RM will also be discussed. Keen or incentives receptiveresourcesvariation their physicochemical possessions in reply to changes in conservational conditions. The physicochemical possessions of such "smart materials" can be altered using a variety of biological, bodily, or biochemical incentives (including pH, infection, enzymes, and ultrasound).

Mechanical ultrasound waves with top frequencies (>20 kHz) can be absorbed and spread through particular media. There are many non-invasive and cost-effective clinical uses for these waves, such as in bioimaging, rehabilitation, make-ups and the nourishmentmanufacturing. In addition, High-Intensity Focused Ultrasound (HIFU) can be employed to cause localized heating, or hyperthermia, in specific areas to cause cell ablation. In addition to the aforementioned uses, drug delivery is quickly becoming an increasingly significant application of ultrasound waves. This is due to the fact that achieving site specificity in drug delivery remains one of the greatest challenges in the field. Ultrasound-responsive carriers present a viable solution to this problem, as they provide a non-toxictrail to facilitate spatiotemporally focused medicine release. As a result, there are numerous biomedical uses for the synergistic use of polymer-basedresources and ultrasound.

Given the invasive nature of ultrasound and the chemical versatility and potential biodegradability of polymeric materials, ultrasound receptive polymeric resourcestake garnered a lot of care. Polymer hydrogels, vesicles, micelles, and bubbles (micro-, nano-, and nano-sized) are all examples of ultrasound-responsive polymer-based materials. These ultrasound-responsive Drug Delivery Systems (DDS) can transport a wide diversity of drugs, countingminor drug particles, proteins, and DNA. Tumor therapy, blood-brain barrier disruptions, illness diagnosis, thrombolysis and transdermal delivery of drugs are just a few examples of the many uses for these vehicles. Drug Delivery Systems (DDS) based on ultrasound-responsive polymers are discussed in this article. After that, we talk about the how, why, and what of preclinical and clinical applications now available. The review concludes with directions for future research to prove the potential of US-RM in drug/gene delivery. The remaining part of this paper is organized are follows: Section II presents an overview of the research focussing on the mechanism of Ultrasound-Induced Drug Delivery. Section III presents an empirical review of Ultrasound Responsive Materials with major focus on Microbubbles (MBs), Micelles, Liposomes and Niosomes. In Section IV, challenges associated with using these materials in delivery systems are discussed. Lastly, Section V draws final remarks and presents directions for future studies.

II. OVERVIEW OF THE RESEARCH

Mechanism of Ultrasound-Induced Drug Delivery

However, the mechanism of ultrasound-induced drug administration remains unclear, despite the extensive study of ultrasound-assisted drug distribution and its therapeutic uses. However, ultrasonic radiation energy certainly plays character in the procedure, both via its current and non-thermalproperties. It is possible to raise the temperature of the

irradiated tissue due to the conversion of acoustic energy into thermal energy, which is what the thermal effect is. The effect is a surge in permeability of the blood vessels and disruption of the cell membranes. With hyperthermia to stimulate drugs' release from thermosensitive liposomes, microbubbles, or polymeric micelles has been considered an effective approach for treating tumors.

Cavitation is the second possible device for ultrasound arbitratedmedicinedistribution and it is the one most commonly associated with the non-thermal effect. Cavitation may be evident in natural cavitation or microbubbles base e.g., nanobubbles or microbubbles. There are two types of cavitation: non-inertial and inertial. The past is characterized by a continuous expansion and contraction of the bubble, and is known as non-inertial (or stable) cavitation. This non-inertial cavitation may be augmented for medical use by ultrasound receptivemanagers (e.g., nanodroplets, nanobubbles, and microbubbles, among others). A phenomenon known as inertial cavitation, also known as transient cavitation, is characterized by the rapid collapse of bubbles, the formation of a high-velocity microstream, as well as the discharge of a free radical. Ultrasound-induced medicationannouncement from drug fullchunk copolymer micelles or vesicles is likely caused by fleecepressure and shockwaves from the failure of foams.

Cavitation action may have some organicbelongings such as sonoporation and increased vascular penetrability. However, sonoporation is a phenomenon wherein irradiated cell membranes become more permeable and porous, allowing for increased intracellular medicationacceptance. This permeability effect is known as sonophoresis or phonophoresis in the field of transdermal drug delivery. Clinical and preclinical studies aiming to safely penetrate the blood-brain barrier are concentrating on improving vascular permeability. One proven method of medicationdistribution to the intelligence involves by means of ultrasound to break down the blood-brain barrier.

To encourage the further advancement of ultrasoundresponsive resources as distribution transmitters, we here review recent successes with original ultrasound receptiveresources (Microbubbles (MBs), Micelles, Liposomes and Niosomes), as well as challenges associated with using these materials in delivery materials.

III. EMPIRICAL REVIEW OF ULTRASOUND RESPONSIVE MATERIALS

Different nanomaterials have been used as US-responsive nanomaterials, and they all have their own unique properties. How nanomaterials react to Ultrasound (US) waves is a key factor in defining their potential future uses. Simply said, the composition of US-responsive nanomaterials is the primary determinant of their method of action. Their diagnostic efficiency, capacity, stability, bioactivity, and biodistribution are all linked to this aspect. In the following sections, we will examine a variety of nanomaterials, including Microbubbles (MBs), Micelles, Liposomes and Niosomes.

Microbubbles

Typically, when people talk about Microbubbles (MBs), they're talking about hollow particles filled with a very particular gas and encased in a very precise layer. Detection of connection amongair bubbles incirculation and loud US echo recorded after a US irradiation marked the beginning of MB development. The most common use of MBs was in echocardiography for the diagnosis of heart problems such myocardial infarction and narrowing of the coronary arteries. The patency of the fallopian tubes, the presence of ureteric reflux, and other medical conditions may all be evaluated using this method. There have been attempts to speed up and improve the efficiency of medical therapy by using MB-mediated US effects to nucleate cavitation in the aimmatter.

In United States, microbubbles have found widespread use as contrast agents in diagnostic imaging. Thanks to their compressible gas-filled core, they may effectively react to US weightsurfs and scatter the affected US liveliness. As a result, they are able to generate waves in sequence, boost ultrasound signals, and improve picture contrast. MBs have been utilized as carriers in US-based medicine and genetic factortransfer systems once full with therapeutic material, they may be followed or drawn to board location by means of US imaging with low-intensity before being affected by the US with high-intensity.Because of microstreaming and ARF, they may release the loaded medications locally and increase the therapeutic agents' depth of penetration into the targeted tissue. Improved gene transfection, therapeutic agent, and anticancer medicine performance may be achieved by using microbubbles. The addition of specific ligands to their surfaces allows for targeted delivery to specific tissues. Theory for creation of MB-based theranosticschemes was provided by a study of MB dynamics and the bodilyvalues underlying MBs by Chen et al. [3]. Recent years have seen a number of articles discussing the use of MBs in theranostics.

Laboratory production of MBs has primarily relied on ultrasonication. Shearing of the liquid medium due to US wave propagation-induced cavitation is the primary mechanism by which MBs are formed. There are two ways to go about the manufacturing process. In the first step, the inner gas that will be encased together with the MB shell precursor is sonicated in a batch sonicator. Second, a continuous sonication is used, in which the inner gas as well as the shell precursor component are sonicated in the same tank at the same time in a constant flow. For MB production, the interface between liquid and gas flows in microfluidic systems has recently been used. When it comes to microfluidic production of MBs, junction and flow concentrating are dual most common techniques. The liquid and gas flows are parallel in the T-junction technique, but are at right angles to one another in the flow-focusing technique because they both emerge from a very narrow opening. Many layers of MBs can be created with the help of microfluidic systems. The physical properties and controllability of the bubbles are additional benefits. The size, shell, and gas composition can all be modified to meet

specific needs. However, the system's production rate is low and inefficient, preventing its rapid transfer to clinical practice.

Improvements in microbubbles' usefulness, efficiency, and characteristics are possible through alteration. Cargo can be transported using various modules throughout the MB framework. In order to load cargo, it is conceivable to generate an oil coatingexclusive the MB. MBs' surfaces can be fullload and customized with targeting ligands. Further opportunities may arise from combining MBs with other NPs. Nanomedicines' uptake, distribution, and accumulation might all be improved by using these hybrids. In theranostics, these have been used for multimodal imaging or for simultaneous imaging and drug delivery. Due to their influence on cellular signaling pathways, microbubbles can stimulate endocytosis. Exocytosis, the process by which intracellular contents are released into the cytoplasm, can be triggered by either US irradiation alone or in combination with MBs, as demonstrated by Barmin et al [4].Initial research on microbubbles led to their use as contrast agents, and later on, they were put to use transporting materials. Their use as theranostic agents has increased in recent years. Numerous studies have demonstrated that combining MBs and US radiation improves the efficiency of medicationdistribution or imagerydifference in the treatment of cardiovascular disease, growth, transferrableillness, mindillnesses, injections, and immunotherapy.

The effects of liposomal-DOX MBs onto the glioblastoma of the human cell exposed to ultrasound (US) at occurrence of 1 MHz were evaluated by Haftcheshmeh et al. [5]. The DOX-containing lipid membranes in this investigation were cross-linked to the surfaces of the MBs using thiol-maleimide. Cell death was increased by a factor of four when DOX-liposomal-MBs were combined with US, compared to when either DOX or DOX-liposomal-MBs were used. They reasoned that was because cavitation events following US amplified intracellular absorption and discharge of DOX into growthcubicles. They demonstrated statistically substantial drug absorption and accumulation in the cytoplasm and nuclei after US treatment in conjunction with MBs. The biophysical principles leading to improved medication delivery are still up for discussion, despite the significant research on MB bubbles in an ultrasonic field.

A chemical influence on the cell membrane is also produced by microbubble oscillations; this time in the form of free radicals that may enhance membrane fluidity and the inflow of Ca^{2+} ions. As shown by Dikalov, Losik, and Arbiser [6], the superoxide radicals scavenger enzyme catalase totally blocked Ca^{2+} flow at lower sonic pressures (50 kPa). In order to determine the mechanism by which an acoustic intensity of 250 kPa enhanced cell permeability and Ca^{2+} inflow, Diesch and Grissmer [7]used verapamil, a particular Ca^{2+} channel blocker, to inhibit the Ca^{2+} -activated K^{+} channel (BKCa channels). They found that at 250 kPa, blocking BKCa channels resulted in a significant influx of Ca^{2+} ions and a resulting increased hyperpolarization of the cellular membranes. They demonstrated that using the maximum pressure (250 kPa), Ca^{2+} did not enter the cytosol via BKCa channels. Apparently, the effects of verapamil at the weakest intensity level used in the United States (50 kPa) were not studied. While free radical scavengers and specific ion path blockers were able to reduce the damage caused by low levels of mechanical stress, they were unable to prevent the damage caused by high levels of mechanical stress. They reasoned that since Ca^{2+} ions entered at the same time; this must be evidence that acoustic pressure causes Ca^{2+} ions to diffuse through the pores in the cell membrane. This conclusion is supported by the fact that the concentration of Ca^{2+} ions inside a cell is inversely proportional to the concentration outside the cell.

Plasma MBs were made by Dong and coworkers by emulsifying plasma gas with surfactant [8]. In reaction to US irradiation, these MBs not only discharged their payload of drug but also produced dynamic radicals e.g., nitric oxide as well as hydrogen peroxide. Furthermore, microbubbles have been used to transport oxygen into the tumor environment. When tumor tissue is exposed to ultrasound (US), the percentage of oxygen (PO2) is increased by almost six times when it is first exposed to oxygen full lipid covered prepping of MBs with combined gas (O2/C3F8 5:1 v/v). Shen et al. [9]found that human mesenchymal cells responded favorably to a combination of lipid-coated MBs as well as low-intensity pulsed US, increasing in both proliferation as well as chondrogenic distinctions. Proliferation of treated cells increased by 40%, while glycosaminoglycan as well as type II collagen production increased by 17 percent as well as 78 percent, respectively. Lysozyme microspheres MBs coated with epidermal growth factor that respond to ultrasound waves were developed by Rees et al. [10], and they demonstrated effective antimicrobial activity, stimulated neovascularization, and sped up the wound healing process.

Multiple studies have looked at the effectiveness of MBs joint with absorbed ultrasound (FUS) in increasing permeability of the blood-brain barriers to enhance the transfer of drugs into the brain system. Some facets of the method have been discussed at length before. The use of MBs in sonothrombolysis has been demonstrated in a few research studies. Using cavitation persuaded US microstreaming to decimate brain plasmamasses is more effective when MBs are present. The application of MBs in cell therapy and gene therapy has been the subject of numerous publications. A potentially effective strategy for enhancing cell-based immunotherapy for cancer may lie in the delivery of genome or immune-stimulatory substances via MBs. Sonoporation and MBs were recently revealed by Mehrad [11]. to increase TRAIL and p53 gene transfection efficiency by 30-50% and trigger apoptosis paths in liver-colouredgrowth cells. These MBs have a positive charge, which makes it possible for them to communicate with nucleic acids. Cationic MB-pDNA hybrids were recently synthesized by Xia et al. [12] using DMAPAP. Their findings indicated that the hybrid framework was stable for up to 30 minutes with acoustic activity comparable to that of MBs.

However, MBs present unique difficulties in their implementation. The endothelial gaps in solid tumor microenvironments range from 380 to 780 nm, yet the comparatively high microsize of MBs (10 m) limits their effective entry into this environment. The fast gas diffusion occurring inside microbubbles, as well as the inherent instability of

conventional lipid shells, contribute to their low quality vivo and shorter circulations of half-life of approximately five to twenty minutes. In addition, the surface of MBs is not readily changed with molecules that are functional to provide drug delivery that is targeted, and the MBs themselves have a limited capacity for drug loading. Following injection, MBs have a very short half-life in circulation before being trapped in the lungs. And there's the risk that the MBs may harm non-intended normal tissues in a way that can't be repaired. Because of this, tumor endothelial as well as cardiovascular targets might be the only ones accessible to US drug deliveryMBs. Fortunately, the rigidity of the MB shell may be adjusted to potentially alleviate these restrictions (based on albumin, phospholipids, and synthetic polymers). When it comes to enhancing the physicochemical characteristics of MBs, Poly(Vinyl Alcohol) (PVA) has been utilized as the shell. Stability of MBs made from PVA is amazing, lasting for months at a time. PVA is a biocompatible material since it does not add any additional toxicity to the complex organism and because it allows for the polymerization of other materials, which facilitates the transport of hydrophobic medicines or DNA. PVA also has better acoustic qualities than MBs do. Tzvetkov et al. [13] have discovered that PVA-based MBs outperform their polymeric-shelled counterparts in linear scattering tests. Temperature also affects the acoustic elements of MBs, e.g., dispersion, attenuation, and backscattering. Similar to other NPs administered systemically, PVA-based MBs are taken up by the reticuloendothelial; nevertheless, they remain in vasculature long enough to function effectively as a contrast agent. For drug/gene delivery and molecular imaging in the United States, scientists have created innovative nanosystems made of liquid PerFluoroCarbons (PFCs), PerFluoroHexane (PFH), halocarbons, and PhosphatidylEthanolamine (PE).

Micelles

When it comes to effective drug delivery, micelles are among the most useful nanocarriers available. When it was found that increasing the concentration of particular surfactants produced particles in the 10-200 nm size range, the concept of micelles was born. Amphiphilic molecules contain micelles, a sort of colloidal dispersion, with the hydrodynamic tails pointing outward into the surrounding water to generate a shell and the thermodynamic heads (typically comprised of carbon chains) pointing inward to form the center of the construct. Micelles are created using van der Waals connections at their center.Micelles can carry both hydrophobic and hydrophilic cargoes, with the former residing in the micelle core and the latter attached to its exterior. The hydrophilic component is not only crucial to the micelles' resistance to degradation or elimination from the outside world, but also to the stability of the structure as a whole. Micelles can be made from both natural and synthetic polymer components, including surfactants.

Micelles can transport a wide variety of molecules, including DNA or RNA aptamers,carbohydrates, peptides, monoclonal antibodies. Micelles may vary in size from 5 to 100 nm, with this range being determined by the nature of the main chain and the lengths of the alkyl groups. Micelles can form in a wide variety of shapes and sizes, based on the form of amphiphilic element, temperature and solute. These include spheres, tubules, rods, lamellae, crewcuts, vesicles, stars, disks, , flowers, toroids, and double-faced micelles. Micelles that are not perfectly spherical are not as robust as spherical ones, but their structure may be cross-linked to increase their stability and render them more amenable to responding to stimuli. Micelles that respond to stimuli may be activated by changes in pH, temperature, enzyme activity, redox potential, illumination, ultrasound, electromagnetic current, or electromagnetism. Enhanced targeting, sensitive particles, magnetic or fluorescent characteristics, and so on are all vital for theranostic usage, and they may all be created by combining micelles with other NPs or macromolecules.

Micelles are formed whenever the concentration of polymer blocks or surfactant molecule exceeds a certain value. The concentration of micellar material below which the system fails is known as the Critical Micellar Concentration (CMC). Ifmicelles' concentration in the solvent is below the critical micelle concentration, the micelles will stay dissolved. In terms of thermodynamic stability, polymeric micelles are in general stable compared to the wetter Michelle because they have a lower CMC. For polymers with more hydrophobic frames, micellar stability can be improved by shortening the hydrophilic frame length and lengthening the hydrophobic sequence. CMC values for surfactant micelles range from 103 to 104 M, while those for polymeric micelles are on the order of 106 to 107 M. As a result of their kinetic stability as well as their thermodynamic consistency, micelles permit prolonged drug release. For the drugs to reach their intended target tissue without being released too soon, it is crucial that the polymeric micelles be both thermodynamically and kinetically stable.

Fatty acid alkyl derivatives of glycerol as well as phosphoglycerol esters are examples of inherently occurring emulsifiers that have been used for micelles. The development of polymeric micelles, nevertheless, has resulted in a shift in focus. You can classify the micelle emulsifiers as either anionic (calcium phosphate, carboxyl groups, sulphides), cationic (generally amine-containing solvents), zwitterionic (phosphocholines, synthesized emulsifiers), or non-ionic (ethoxylate, glucoside). As a result of their enhanced targeting ability, consistency, long-term transmission, protein assimilation, sustained and controlled release of drugs, greater molecular mass, slower depersonalisation rate, degradability, better infiltration, higher drug bioavailability capacity, and enhanced pharmacodynamic and pharmacokinetic profile information, microspheres have found widespread use in a variety of biological application domains. Furthermore, polymeric micelles are replacing surfactant microemulsions in pharmaceutical preparations because their CMC value is reduced.

Polymeric micelles are made up of many types of polymers, such as diblock copolymers, triblock copolymers, and graft polymeric materials. Most typically, amphiphilic diblock or triblock polycaprolactone are utilized. Polymers are

chosen with consideration given to their hydrophobic core composition, cytocompatibility, degradability, liquidity, increased bioavailability, and degradability. Micelle properties are investigated with respect to the interfacial tension of the blocks in the solvents, connections between copolymer, temperatures, and compounds.The drug-reservoir core of the polymeric micelles is surrounded by an inhibitory shell (corona) that also improves colloidal stability and slows down excretion in the body. Many experiments use pluronic polymer micelles, making them a popular choice. Triblock copolymers comprising hydrophobic polyether oxides block and hydrophilic poly (ethylene oxide) blocks make up pluronic micelles. Pluronic P105-based micelles are the most commonly utilized US-triggered drug delivery agents.

Micelles can release a variety of cargos after being exposed to the US, and this process has been described in many papers. Cavitation processes have been proposed to account for the release of cargo from micelles during ultrasonication. Shear forces exerted on the micelles as a result of cavitation and bubble development and collapses result in the release of cargo. Furthermore, it is well established that ultrasonication triggers endocytosis and pinocytosis operations and causes disruptions in the cell membrane, hence facilitating the reception of the discharged cargos by the designated cells. After US exposure ends, the released cargoes may be re-encased. Furthermore, ultrasonication-induced hyperthermia enhances the micelle destruction overall and, potentially, cargo release. The use of US alone or US-responsive micelles, as demonstrated by Liu and Lang [14], can improve chemotherapy. Their research demonstrated that the sonicated tissues and cells accumulated more of the targeted drug and micelles. In addition, they stated that the intensity of the US was more important than the duration in determining the drug discharge rate from micelles. In a similar vein, Baldelli et al. [15] showed that shorter durations between pulses led to the possibility of re-encapsulation of drugs might mitigate the negative implications of any stray medication.

Polymeric micelles that respond to redox and the HIFU potential were described as a new manufacturing technique by Motamedi et al, [16], suggesting that this system might be used as nanocarriers for pyrene delivery as a prototyped cargo. This two-part arrangement was composed of biodegradable Poly(Ethylene Glycol) (PEG) and Poly(Lactic Acid) (PLA) block copolymers linked by a disulfide bond that was broken by HIFU radiotherapy or reducing chemicals like glutathione. The scientists stated that HIFU illumination in conjunction with glutathione treatments resulted in the implosion of cavitation MBs due to a solvodynamic shear stress, which in turn caused the disulfide connection to be severed at a precise place, micelles to be disrupted, and the entrapped pyrene to be released from the PLA and PEG blocks in a controlled, irrevocable manner.

To the same end, another team looked into how different poly(2-oxaline) micelle compositions released dexamethasone. They found that the quantity of medicine released was increased by 6-105%, dependent on the copolymer used, the amount of drug contained, and the length of time the capsule was stimulated. In a different investigation, docetaxel-loaded amphiphilic hyaluronic acid micelles were synthesized. They found that the micelles' diameter grew after being exposed to HIFU, that the micelles disintegrated under HIFU, and that cell uptake of the particles rose as a result of changes in the permeability of the cells.

Sonic wave treatment has also made use of micelles. By studying the additive effects of epirubicin conjugated polymer microspheres NPs, O'Neill and Li [17] explored the viability of cyclic HIFU as a theranostic medicine for the chemotherapy of cancer.Although the encapsulated medication served as a sonosensitizer, in this system, the hydrophobic layer of the micelles shielded it from ROS production that was triggered by US irradiation. Possible results of using US to treat cancer include thermal and mechanical effects on the cell, the generation of anticancer medications, and the development of reactive oxygen species (ROS) that destroy cells.After being exposed to UV light from the United States, they checked for the presence of hydroxyl and superoxide radicals. In their opinion, epirubicin degeneration might be brought on by hydroxy radicals. They noted a clear correlation between the intensity of US irradiation and the production of hydroxyl radicals, even during very brief exposure times. Epirubicin's ability to generate superoxide radicals in response to US illumination suggests that the micellar structure (NC-6300) may act as a sonosensitizer to produce even more oxidizing ions in solution.At doses of 20 M, hydroxyl radical and oxidant anions induced death in cells.

Micelles have also been used in the sonodynamic treatment of several canine malignancies, including as osteosarcoma, prostate cancerchondrosarcoma, and hepatocellular carcinoma, as proven by Horise et al. [18]. Epirubicin-loaded NC-6300 micelles were employed as anticancer sonosensitizers and shown synergy with HIFU irradiation in this study. The tumor accumulated NC-6300 micelles owing to the Enhanced permeation, and US stimulation resulted in efficient ROS production from these tumor-bound micelles.Two weeks following sonodynamic treatment, the chondrosarcoma dog's tumor had shrunk by 85%, and the dog could walk and run again, although this had not been the case previously. Although the osteosarcoma dog's tumor shrank very little, the animal had far less discomfort. Tumor development in patients with hepatocellular carcinoma remained, although at a slower pace than before sonodynamic treatment was administered. After the operation, both the calcified mass and the lung metastasis that had been present in the dog with prostate cancer were no longer present. Although the HIFU irradiation power was less than that of standard HIFU treatment, it is possible that this is what caused the calcified mass to dissolve. Chen, Hsu, and Lio [19]speculated that the immunological response that followed the sonodynamic treatment may be responsible for the unexpected elimination of the lung metastasis. Micelle-based sonodynamic therapy showed promise in their study, suggesting more research is needed. In addition, the production of MBs during US irradiation was able to boost contrast in US imaging using their technique.

Micelles filled with nitric oxide donors that were activated by high-intensity focused ultrasound were created by Zhang et al. [20]. Nitric oxide (NO) gas was generated by the pyrolysis of bis- (trimethylphenyl) imidazolylidene nitric oxide

(IMesNO), which served as the NO-donor. Micelles packed with IMesNO increased drug concentration at the tumor location through the EPR action.First, NO was generated in response to ultrasound irradiation, which resulted in vasodilation and, ultimately, an upsurge in drug-loaded micelles aggregated in tumor arteries.

Liposomes

Like cell membranes, liposomes have two phospholipid layers that encapsulate a lipid bilayer. Phospholipids are amphiphilic compounds consisting of a hydrophilic head attached to a hydrophilic long hydrocarbon chain(s). Despite the fact that lipid membranes are the primary component of lipid nanoparticles, sterol and other polymeric blocks may also be included. Lipid membranes may self-assemble into a variety of forms when subjected to the action of water. The edges electrostatic interaction caused by the disproportionate availability of nonionic carbon chain to the aquatic phase is reduced to a minimum during the creation of vesicles as well as the folding of lipid bilayers, making vesicles the most robust nanostructures possible.The physicochemical qualities of liposomes are dependent on factors such as their manufacturing process, lipid variety and charge,biological solvent,surfactant,lipid content, as well as osmotic vitality of the suspended media. The style of preparation determines whether or not multilayer liposomes are formed. Methods include reverse phase evaporation, detergents depletion, freeze-thawing, lipids hydration, and alcoholic inoculation are some of the typical forms of making vesicles.

In addition, microfluidic-based preparation techniques enable a scalable manufacture of tiny, homogenous liposomes. It is the amphiphilic nature of liposomes that allows them to encapsulate both lipophilic and hydrophilic compounds. Liposomes have the ability to compartmentalize hydrophilic compounds in their interior space while enclosing lipophilic ones in their lipid bilayer. Liposomes are capable of being modified to react to external cues. Having this option would be helpful in ensuring that cargo is only released at the designated locations. In order to release their contents, liposomes may be stimulated by ultrasound, light, heat, or changes in pH. It is possible to make magnetically and electrically sensitive liposomes by combining them with other materials. While it's true that these nanoparticles are generally safe to use and pose no pharmacological risks, their toxicity may vary depending on factors including how long they're in the body, how much cholesterol they have, their charge, and the saturation and length of the fatty acids they contain. When used with drugs, liposomes may improve their efficiency. Drugs having a longer half-life in circulation after being encapsulated in liposomes are more likely to reach their intended targets in solid tumors having faulty vasculature because to this "EPR effect." Still, it's difficult to phagocytose them while they're circulating in the blood. Targeting liposomes with surface ligands improves the efficiency of cargo delivery while reducing the likelihood of unwanted systemic consequences.

Conventional Liposomes

Despite the fact that the basic mechanism of drug delivery from liposomes is not fully known, several investigations have shown that US can induce drug release from liposomes. It is possible that the release is mediated by a number of distinct processes, each of which is sensitive to variations in US variables and the liposomes' biochemical structure. Cavitation, thermal impacts, and acoustic streaming are the most likely methods for drug delivery from these structures, and they may overlap to some extent.

As was previously mentioned, cavitation occurs when a vapor bubble forms similar to or within the liposome's bilayer of lipids and then suddenly deflates. When using DDS, the delamination pathway should be powerful enough to rupture the lining and release the liposomal components. Recent studies have shown that low-frequency ultrasound can end up causing cavitation, which can rupture liposomes and speed up the release of their cargo.Three encapsulated medicines, doxorubicin, methylprednisolone hemisuccinate, and cisplatin, were shown to be released by low-frequency (20 kHz) US in a study by Zhao, Guo, Tang and Bao [21]. US exposure for up to 180 s induced an effective release of pharmaceuticals from liposomes (80%), and this was independent of the drug type or the manner of drug delivery. About 20percent of the lipid nanoparticles were found to have irreversibly broken down, while the other 80percent had developed temporary holes. DOX was found to be released from lipid nanoparticles in the framework of 1 MHz cyclic US frequency by Gomes et al. [22], who hypothesized that this might be to shield the lipid membranes from the potentially harmful temperature variations caused by US disclosure and to take advantage of the microbubble implications.Liposome payload release following exposure to the US may also be explained by an increase in temperature. If it were due to the thermal impacts of US, the drug discharge rate would be more gradual, and the liposomes' permeability might be enhanced if the local temperatures climbed over the lipid state transition point.

Lentacker et al. [23] investigated a TSL formulation with a Tm slightly higher than 37°C, which caused drug release with little hyperthermia. When comparing the DOX release efficiency between the fluid and gel-like compressed liposome states, the gel-like condensed form (organized packing) was shown to be superior. Increased susceptibility of the border flaws during the phase transition was identified as the mechanism. For fast drug release and local DOX administration to tumors, Thedrattanawong, Thanapongpibul, Nittayacharn, and Nasongkla [24]similarly employed pulsed HIFU to activate TSLs. An up-to-date investigation demonstrated the potential function of acoustic streaming in the effective release of drugs from lip nanoparticles. Wang et al. [25] indicated that the release of condensed cargo in response to ultrasonication is dependent on the hydrophilicity or hydrophobicity of the cargo itself. It has been found that non-cavitational and non-thermal actions of US are responsible for the release of hydrophilic cargo. It has been postulated that hydrophobic cargo inside lipid bilayers is released during US exposure because to particle collisions generated by radiation forces.

In accordance with Qiang and Doherty's [26] research, solid NPs trapped in liposomes may be able to move in response to US waves, leading to membrane disruption. This reaction to ultrasound was not caused by cavitation, but rather by the ultrasound's mechanical impacts, and these novel lipid nanoparticles were more resilient compared on encased gas cores. High-frequency ultrasound (>1 MHz) combined with Poly(Lactic-co-Glycolic Acid) (PLGA) liposomes have been utilized to controllably release mitoxantrone. They found that using ultrasound to activate liposomes caused the lipid membranes to break, releasing the mitoxantrone molecules within.

TSLs combined with HIFU have been described lately as a noninvasive image-guided medication delivery method for the administration of anticancer treatments. This is because ultrasound-induced hyperthermia has the potential to drastically alter the porosity of the tumour vascular and increase nanoparticle absorption. In 2018, scientists revealed TSLs that contained the chemotherapeutic medication topotecan (Hycamtin®), whose release in the tumor could be tracked by a rise in the agent's intrinsic fluorescence. To facilitate simultaneous Near-Infrared Fluorescence (NIRF) and MRI liposome tracking, a novel DDS-centred on TSL tag with imaging agents was developed in this study. By increasing localized flow of blood and diminished interstitial tumor pressure, nanoparticle concentration inside the tumor was increased using localized moderate hyperthermia (43 ℃). This method improved delivery of NP with dimensions of approximately 390 nm. Using MR thermometry, we found that Focused Ultrasound (FUS) induced profound, localized hyperthermia. Activating drug discharge from the carriers and increasing NP accumulation in the tumor might be the result. With the use of NIR imaging, we were able to see that TSL was accumulated selectively in the tumors. The absorption of the TSLs was significantly improved by mild hyperthermia caused by FUS (3 minutes at 40 ℃, 33 minutes once i.v. injection has been provided). Fast US-responsive drug delivery was also indicated by the colocalizations of topotecan fluorescent emission, which was found immediately after FUS administration. It was hypothesized that applying a second moderate hyperthermia treatment 1 hour after the first would boost TSL buildup and parallel topotecan release. In addition, in vivo MRI was used to confirm the increased uptake of TSLs after FUS therapy.

Antibodies and ligands may be added to liposomes to make them more effective targeting vehicles. The method improves therapeutic or diagnostic success while decreasing the risk of systemic adverse effects. Human Epidermal Receptor 2 (HER2) development component of the positive breast tumor cells were targeted in research using a functionalized form of the liposomal delivery vehicle calcein and doxorubicin. Due to their elevated levels of HER2 receptor surface expression, these cancer cells are more likely to interact with trastuzumab-functionalized liposomes than normal cells. For medication delivery, liposomes were exposed to Low-Intensity Focused Ultrasound (LIFU). Adding LIFU to liposomal trastuzumab enhanced treatment results, as shown by increaseddrug absorption cell toxicity by the HER2positive membrane. HeLa cells were targeted in a previous investigation using transferrin-functionalized calcein-loaded liposomes. Furthermore, the therapeutic efficiency of therapy was enhanced by a synergistic interaction between the distribution of LIFU and the targeting qualities. Results were similar in research that combined LIFU with calcein lip nanoparticle operational with the serum albumin for breast cancer treatment. These researches show the importance of the interaction between LIFU and targeted qualities for a more effective treatment result.

Thébault et al. [27] recently proposed a novel therapy method including the magnetic agglomeration of Ultra-Magnetic Liposomes (UML), accompanied by HIFU to trigger the production of an antivascular medication, while MRI monitored the process.To create a thermosensitive CA4P-UML, they enclosed the vascular disrupting chemical combretastatin A4 phosphate (CA4P) in the center of a UML. The consequences of this method were examined by studying CT26 colon cancers in mice. After 24 hours of treatment, the combination treatment showed significant advantages, including a 150-fold increment of the antitumor response than chemotherapy response.

Echogenic Liposomes

Ultrasound imaging now has a targeted contrast agent thanks to the development of large echogenic liposomes. Smaller than a micron in size, liposomal particles that contain gas or a chemical that may be converted into gas. A gas bubble within a liposome can be interpreted thermochemically in two ways: either as a hydrophilic drug sandwiched between two different monolayers of the liposomes, or as a bubble of gas in the interior compartment of aqueous liposomes that is covered by the monolayer. Heavy, bio-inert gases such as perfluorocarbons as well as fluorinated gases are also common, in addition to oxygen and nitrogen. Particles' crystallinity, physiological half-life, as well as echogenicity are all affected by the interior core gas as well as the shell components inside the body. The half-life of MBs in circulation may be lengthened by the presence of strong gases, which may reduce gas diffusion and gas leak from the inner structure of the lipid nanoparticles into the fluid medium. Whether or not gas encapsulation is successful depends on a number of factors related to lipid shell as well as compressed gas, including the diffusion of gas over the lipid shelling, lipid shell thicknesses, MB size, and the availability of blood or protein in the mediums.

Distinct techniques have been used to produce three several echogenic liposomal structures. The first design features a gas- and monolayer-enclosed smaller compartment, with the aqueous component located in a larger, monolayer-free compartment. Freeze lyophilization or pressure freezing are two methods that may be used to create these echogenic liposomes. In the second arrangement, the liposome's aqueous center contains a gas bubble encapsulated by a monolayer. It is possible to make PEG-liposome-modified bubble liposomes using the reverse stage evaporation method. In a bath sonicator, the liposomal elements are mixed with perfluoropropane gases and sonicated. Finally, a complex compound has been constructed wherein standard lipid bilayers are joined to stabilized air pockets through a biotin-avidin bond.

After US irradiation of hypoechoic particles, four results are conceivable according to the particles' physicochemical characteristics: As the echogenic liposomes decrease, the gas either (1) diffuses away from them, (2) US illumination may cause shell cracks allowing the gas to be eliminate (3) There are less particles produced when using echogenic nanostructures, or (4) fast disintegration of echogenic pieces causes shell material to separate from the active interior core. Echogenic liposome responses to ultrasonication are affected by liposomal compositions, encapsulated gases, and US factors. How liposomes respond to US is influenced by their pliability, which in turn affects what happens to them after ultrasonication. Lipid-encapsulated MBs could fluctuate and re-assemble quickly, but nanoparticles with hard or inflexible shells would shatter under the powerful ultrasound. So, ultrasound can cause gas-filled liposomes to swell to more than 10 times their original surface area before they destabilize and coalesce.

Though hydrophobic drugs are capable of being contained in echogenic liposomes, it is likely that they will be refractory to US-induced ejection since they are more widely dispersed in the phospholipid bilayer than in liquid.The drug may also persist in the liposome's lipid shards after it has been broken apart. Combining hydrophobic medications with cyclodextrins, which are characterised with hydrophilic outer surface and form a compound with hydrophilic pharmaceuticals via the hydrophobic interactive pockets, is one way to circumvent this problem and make hydrophilic drugs more hydrophilic.

They could be covalently linked with MB to make US-responsive lipid membranes. US-responsive domains for cancer treatment based on liposome-macrophage prodrugs have been discovered recently.However, their size prevents them from penetrating tumors effectively, and thus far they have only been studied as passive carriers. Chandan and Banerjee [28]revealed in 2018 that phosphatidylserine-centered paclitaxel-liposome-nanobubble conjugates (PSPLBC) with a submicron size (756 180.0 nm) exhibit a pro-apoptotic anticancer impact and also provide image guiding. Ultrasound-mediated cavitation triggered drug discharge from the PSPLBC. Internalization by cells increased by a factor of 10 in in vitro experiment when contrasted to a control sampling. In additional, the remarkable anticancer activity shown in vitro (98.3 0.8% tumor development suppression) and in vivo (CI 0.1) was a result of the significant synergism among polystyrene (PS) and paclitaxel.

Submicron sized nanobubble-paclitaxel liposome complexes (528.7 31.7 nm) have been created by Yin et al. [29] for use in ultrasound scanning and ultrasound-responsive administration of drugs in cancerous cells. An impressive 85.4 percent of the paclitaxel was successfully entrapped in the nanobubbles, and the 200 nm liposomes bonded to the nanobubbles with a high degree of efficiency (conjugation effectiveness: 98.7% 0.14%).After being exposed to US irradiation, liposomes were taken up by cells at a rate that was two times more that the lipid nanoparticles. The drug's therapeutic efficacy has been improved by over a factor of 300 as a result. Also, when compared to SonoVue, a commercially available contrast agent in the United States, nanobubbles were found to have superior echogenic stability.

Lip-AIPH defined by Ding et al. [30] was concentrated with dual 2-azobis dihydrochloride and was able to create gas bubbles instantly while also producing a high concentration of Reactive Oxygen Species (ROS) when exposed to UV light. Gas and free radical generation did not seem to be oxygen concentration dependent in in vivo tests. Furthermore, this setup has the potential to improve sonodynamic treatment in a hypoxic tumour environment. Confocal imaging was used to observe the MCF-7 cells' real-time reaction to the gaseous MBs after they were gradually treated with Lip-AIPH while being exposed to US illumination.As the duration of US irradiation rose, so did the amount of gas bubbles around the cells. After being subjected to US therapy, cells gradually lost their normal shape and perished as a result of cavitation induced by the US shock, which caused gas bubbles to burst.

Gas may also be used to make liposomes US-reactive. Echogenic argon-filled soy liposomes were created by Chen et al. [31], and were encapsulated with 5-fluorouracil. About 65% of 5-fluorouracil might be made available with LIFU administration. The US-responsive response is caused by an expansion of the internal structure gas after exposure to the US with the rupture of the lipid nanoparticles.This method may lessen systemic toxicity (particularly to bone marrow) and boost the therapeutic factor.

Echogenic exosomes derived from bovine milk were employed to improve the contrast of ultrasonography in a first-of-its-kind study. Natural cellular interaction and biomolecule delivery occur through exosomes, which are extracellular bilayer vesicles. Advantages over traditional liposomes include low immunogenicity and zero toxicity. These echogenic exosomes were shown to have strong linear and nonlinear scattering responses, making them promising candidates for application as ultrasound-responsive pharmaceutical distribution systems.

Niosomes

Niosomes, like liposomes, are vesicles composed of a bilayer of non-ionic surfactant. These receptacles may have one or more layers, and they often have two. Concentric vesicles nestled within one another characterize multilayered vesicles. Amphiphilic structures including alkyl glyceryl ethers, alkyl ethers, polyoxyethylene,polysorbates, and terpenoids ethers are employed as non-ionic surfactant in niosomes. These render the niosomes more impermeable by preventing vesicle agglomeration and the gel-to-liquid phase transition.

Niosome production follows a similar basic principle to liposome creation. Structured vesicles are formed when amphiphilic chemicals self-assemble. However, the provision of more energy would speed up this process. Thermodynamically stable niosomes need the use of optimal combinations of detergents and charge-inducing chemicals. To create niosomes with the desired characteristics, it is necessary to control for a wide range of variables, including

monomer content, hydration temperature, hydration duration, pH of the medium of hydration, cholesterol, cosurfactant, aqueous interlayer, lipid chain length, chain-packing, drug type, and membrane asymmetry.

The preparation process matters since it affects the vesicles' physicochemical characteristics and pharmacokinetics. Niosomes may be synthesized using many processes such as thin-film hydrations, sonications, ether injection, reverse cycle evaporation, heating, rehydration/dehydration, and freeze-thaw. Niosomes produced using microfluidics would be more consistent and of predetermined size than those prepared using the aforementioned bulk approaches. Entrapment efficiency, sizes, preferred materials, homogeneity, drug-loading process, and layers are all critical factors, which might be considered while deciding on a certain production process.

The purpose, vesicle sizes as well as strategy of preparationare the three major criteria used to categorize niosomes. Niosomes can be broken down into three main categories, denoted by their size and number of layers: Smaller Unilamellar Vesicles (SUV), Multilamellar Vesicles (MLV), and Larger Unilamellar Vesicles (LUV). Submicron dimensions characterize the vast majority of niosomes. SUVs have particles with a size of around 10–100 nm, LUVs of around 100–3000 nm, and MLVs of around 5 micrometers or more. There have also been reports of giant vesicles.

The shortcomings of liposomes prompted interest in niosomes. Niosomes have several advantages over traditional liposomes, including increased chemical constancy, decreased toxicity,prolonged shelf life, osmotic activities, easy surface alteration, increased compatibility, biodegradability, and reduced immunogenicity. Other benefits of niosomes include their osmotic activities, long storage duration, characteristics that can be controlled, and relatively simple production process. Nonetheless, like liposomes, niosomes can experience instability and cargo leakage. Niosomes can carry drugs that are either hydrophilic or lipophilic, or both. Several factors, includingvesicle sizes, morphology, vesicle discharge, stability, permeability, encapsulation efficiency, as well as the release profile, should be considered in DDS. Peptides' and proteins' delivery as well as chemotherapy for cancer and HIV/AIDS have all made use of niosomes. The niosomes can be injected intravenously, applied topically, swallowed, injected into the eye, or breathed in through the lungs.

Leelarungrayub, Manorsoi, and Manorsoi [32]looked into the feasibility of using ultrasound to activate niosomes, which contain drugs. Niosomes were created by encapsulating carboxyfluorescein and afterwards sonicating them; the researchers then determined the quantity of carboxyfluorescein in the nanoparticles and the adjacent media. Because the quantity of carboxyfluoresceine enclosed reduced by two-fold although it grew by 10 percent in the liquid, Shinu et al. [33] inferred that the medication may pass the membranes without appreciably damaging the niosomes or affecting their size and distribution.Niosomes were also used to encapsulate Plai oil for a different study, which showed that when combined with US irradiation, the two treatments had synergistic effects on anti-inflammatory activity compared to the control group. They hypothesized that cavitation was to blame for the drug release. Hyperthermia is another potential mechanism for drug delivery from nanoemulsion after contact with US. Lu and Ten Hagen [34] investigated release of drug at 25℃ , 37℃ , and 42 ℃ using a thermo-responsive niosome manufacturing technique. They showed that release was facilitated by temperatures of 42 degrees Celsius, suggesting that hyperthermia induced by ultrasound (US) could be pertinent.

IV. CHALLENGES ASSOCIATED WITH USING THESE MATERIALS IN DELIVERY SYSTEMS

Treatments for cancer, coronary disease, orthopaedic disease, ophthalmic disease, neurological disease, and vaccine inoculation have all benefited from the study and application of Ultrasound-Responsive Materials (US-RM) for drug/gene delivery.However, there are obstacles that must be overcome before US-RM can be widely used in drug/gene delivery.

First, adequate drug/gene delivery and release in sick tissues is a must for successful disease treatment.In order to be effective, ultrasound-reactive materials often have an ultrasound-reactive structure. In ultrasound responsive materials (Microbubbles (MBs), Micelles, Liposomes and Niosomes), these ultrasonic sensitive structures take up a lot of space, reducing the amountof drug/gene-loaded materials, reducing the amount of drug/gene carried to sick organs, and limiting the therapeutic efficacy.Second, whereas microbubbles are superior at responding to ultrasound, nanoscale US-RM offer benefits in the targeted delivery of medications and genes. In order to produce cavitation in nanoparticles and facilitate the efficient release of drugs/genes from nanomaterials, a greater ultrasonic intensity is required. However, high-intensity ultrasound has been shown to harm adjacent healthy tissues. Because of the quick collapse and subsequent discharge of drug or gene with bubbles, high-intensity US might not be suitable for medications that need a prolonged release period.

In particular, issues with ultrasonic frequencies persist. Damage to biological tissues may occur when sonication-induced temperature increase is significant, and this is due to the irreversible pore creation on cytoplasmic membrane at both low and high frequencies. As a result, it is important to regulate both the duration and intensity of ultrasound sonication. Pulsed-focused ultrasound, as discovered by Chu et al. [35], causes the blood-brain barrier to open, which is followed by high productivity of heat-shock proteins, tumor necrosis factor, interleukin-18, interleukin-1, as well as brain tissue inflammation, showing that more care should be considered when using US-RM drug or gene delivery systems in the brain.

V. CONCLUSION AND FUTURE RESEARCH

Drugs and genes may be delivered to particular tissues through ultrasonic-responsive materials, which are activated by ultrasound sonication to release their contents. On the other hand, in vivo and in vitro researches on animals have provided the bulk of the data to far. Ultrasound-Responsive Materials (US-RM) may be useful for drug/gene delivery systems; nonetheless, this has not yet been proved in various clinical researches. In that case more research is require in order to prove the capacity of US-RM in drug or gene delivery. New research shows that the lack of drugs or genetic material in

US-RM is the main factor preventing their wider use. There will be a "sweet spot" for clinical translation of US-RM that involves boosting the drug/gene-loaded content of these materials. Also, it is generally agreed that sonoporation is the primary mechanism by which US-RM facilitate the release of cargoed drugs/genes. There are a number of different effects that may be brought about by ultrasound when it comes into contact with ultrasonic-responsive materials, including mechanical forces, sonoporation, heating, and sonochemical reactions. For this reason, developing US-RM in drug/gene delivery will benefit greatly from a deeper understanding of how US-RM improve the release of loaded drugs/genes.

Data Availability
No data was used to support this study.

Conflicts of Interests
The author(s) declare(s) that they have no conflicts of interest.

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References

[1]. D. Fu et al., "A novel redox-responsive ursolic acid polymeric prodrug delivery system for osteosarcoma therapy," Drug Deliv., vol. 28, no. 1, pp. 195–205, 2021.
[2]. C. A. Franco-Urquijo, J. Á. Navarro-Becerra, A. Ríos, and B. Escalante, "Release of vascular agonists from liposome-microbubble conjugate by ultrasound-mediated microbubble destruction: effect on vascular function," Drug Deliv. Transl. Res., vol. 12, no. 5, pp. 1175–1186, 2022.
[3]. H. Chen, D. Evangelou, K. Loskutova, M. Ghorbani, and D. Grishenkov, "On the development of a novel contrast pulse sequence for polymer-shelled microbubbles," IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 68, no. 5, pp. 1569–1579, 2021.
[4]. R. A. Barmin et al., "Engineering the acoustic response and drug loading capacity of PBCA-based polymeric microbubbles with surfactants," Mol. Pharm., vol. 19, no. 9, pp. 3256–3266, 2022.
[5]. S. M. Haftcheshmeh et al., "Liposomal doxorubicin targeting mitochondria: A novel formulation to enhance anti-tumor effects of Doxil® in vitro and in vivo," J. Drug Deliv. Sci. Technol., vol. 62, no. 102351, p. 102351, 2021.
[6]. S. Dikalov, T. Losik, and J. L. Arbiser, "Honokiol is a potent scavenger of superoxide and peroxyl radicals," Biochem. Pharmacol., vol. 76, no. 5, pp. 589–596, 2008.
[7]. A.-K. Diesch and S. Grissmer, "Kinetic aspects of verapamil binding (on-rate) on wild-type and six hKv1.3 mutant channels," Cell. Physiol. Biochem., vol. 44, no. 1, pp. 172–184, 2017.
[8]. C.-Y. Tsai, L.-W. Teng, M.-C. Chang, Y.-P. Tseng, and L. I, "Solitary wake field microdynamics of the pulsed laser induced microbubbles in three-dimensional dusty plasma liquids," Phys. Plasmas, vol. 16, no. 6, p. 063702, 2009.
[9]. J. Shen et al., "Overexpression of PYGO1 promotes early cardiac lineage development in human umbilical cord mesenchymal stromal/stem cells by activating the Wnt/β-catenin pathway," Hum. Cell, vol. 35, no. 6, pp. 1722–1735, 2022.
[10]. C. O. Rees et al., "OP06.01: Quantitative ultrasound measurement of endometrial waves in adenomyosis versus women with normal uteri: the WAVES study," Ultrasound Obstet. Gynecol., vol. 60, no. S1, pp. 64–64, 2022.
[11]. H. Mehrad, "Effect of HDL- loaded pesda microbubbles- mediated focused shock wave sonoporation therapy on biomechanical parameters in an experimental animal model of abdominal aorta fibroatheromatic plaque," Atherosclerosis, vol. 355, p. 244, 2022.
[12]. Y. Xia et al., "Corrigendum to 'Enhancement of flotation response of fine low-rank coal using positively charged microbubbles' [Fuel 245 (2019) 505–513]," Fuel (Lond.), vol. 250, p. 381, 2019.
[13]. G. Tzvetkov, P. Fernandes, S. Wenzel, A. Fery, G. Paradossi, and R. H. Fink, "Soft X-ray induced modifications of PVA-based microbubbles in aqueous environment: a microspectroscopy study," Phys. Chem. Chem. Phys., vol. 11, no. 7, pp. 1098–1104, 2009.
[14]. T. Liu and M. Lang, "Preparation and characterization of novel functional tri-block copolymer for constructing temperature/redox dual-stimuli responsive micelles," J. Macromol. Sci. Part A Pure Appl. Chem., vol. 59, no. 8, pp. 513–525, 2022.
[15]. A. Baldelli et al., "Engineered nasal dry powder for the encapsulation of bioactive compounds," Drug Discov. Today, vol. 27, no. 8, pp. 2300–2308, 2022.
[16]. S. Motamedi, B. Massoumi, M. Jaymand, H. Derakhshankhah, and E. Alizadeh, "Bioreducible and pH-responsive shell crosslinked polymeric micelles from a star-shaped terpolymer as drug delivery system," Int. J. Polym. Mater., vol. 71, no. 7, pp. 481–492, 2022.
[17]. B. O'Neill and C. Li, "Translational studies of the effects of pulsed HIFU using a modified clinical MR guided focused ultrasound device," FocUS Archive, 2018.
[18]. Y. Horise et al., "Sonodynamic therapy with anticancer micelles and high-intensity focused ultrasound in treatment of canine cancer," Front. Pharmacol., vol. 10, p. 545, 2019.
[19]. H.-Y. Chen, M. Hsu, and C.-W. J. Lio, "Micro but mighty-Micronutrients in the epigenetic regulation of adaptive immune responses," Immunol. Rev., vol. 305, no. 1, pp. 152–164, 2022.
[20]. M. Zhang et al., "Application value of contrast-enhanced ultrasonography in the treatment of uterine fibroids by high-intensity focused ultrasound ablation: A retrospective study," J. Clin. Ultrasound, 2022.
[21]. Zhao Y., Guo J., Tang H., and Bao X., "Intratympanic methylprednisolone hemisuccinate injection in treating the refractory noise induced deafness," Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi, vol. 33, no. 7, pp. 547–548, 2015.
[22]. E. R. Gomes et al., "Fusion of tumor-derived exosomes with long-circulating and pH-sensitive liposomes loaded with doxorubicin for the treatment of breast cancer," AAPS PharmSciTech, vol. 23, no. 7, p. 255, 2022.
[23]. I. Lentacker, B. Geers, J. Demeester, S. C. De Smedt, and N. N. Sanders, "Tumor cell killing efficiency of doxorubicin loaded microbubbles after ultrasound exposure," J. Control. Release, vol. 148, no. 1, pp. e113-4, 2010.

[24]. C. Thedrattanawong, C. Thanapongpibul, P. Nittayacharn, and N. Nasongkla, "Reduction the initial-burst release of Doxorubicin from polymeric depot as a local drug delivery system for cancer treatment," Annu Int Conf IEEE Eng Med Biol Soc, vol. 2018, pp. 4221–4224, 2018.
[25]. H. Wang et al., "Application of ultrasonication at different microbial growth stages during apple juice fermentation by Lactobacillus plantarum: Investigation on the metabolic response," Ultrason. Sonochem., vol. 73, no. 105486, p. 105486, 2021.
[26]. W. Qiang and K. E. Doherty, "Model phospholipid liposomes to study the β-amyloid-peptide-induced membrane disruption," Methods Mol. Biol., vol. 1777, pp. 355–367, 2018.
[27]. C. J. Thébault et al., "In vivo evaluation of magnetic targeting in mice colon tumors with ultra-magnetic liposomes monitored by MRI," Mol. Imaging Biol., vol. 21, no. 2, pp. 269–278, 2019.
[28]. R. Chandan and R. Banerjee, "Pro-apoptotic liposomes-nanobubble conjugate synergistic with paclitaxel: a platform for ultrasound responsive image-guided drug delivery," Sci. Rep., vol. 8, no. 1, 2018.
[29]. T. Yin et al., "Tumor-penetrating codelivery of siRNA and paclitaxel with ultrasound-responsive nanobubbles hetero-assembled from polymeric micelles and liposomes," Biomaterials, vol. 35, no. 22, pp. 5932–5943, 2014.
[30]. H. Ding et al., "A novel nano material for anti-cerebral ischaemia: preparation and application of borneol angelica polysaccharide liposomes," J. Liposome Res., pp. 1–10, 2022.
[31]. C. Chen et al., "Method for loading liposomes with soybean protein isolate hydrolysate influences the antioxidant efficiency of liposomal systems: Adding after liposomes formation or before lipid film hydration," Food Hydrocoll., vol. 129, no. 107629, p. 107629, 2022.
[32]. J. Leelarungrayub, J. Manorsoi, and A. Manorsoi, "Anti-inflammatory activity of niosomes entrapped with Plai oil (Zingiber cassumunarRoxb.) by therapeutic ultrasound in a rat model," Int. J. Nanomedicine, vol. 12, pp. 2469–2476, 2017.
[33]. P. Shinu et al., "Recent advances and appropriate use of niosomes for the treatment of skin cancer," Ind. J. Pharm. Educ., vol. 56, no. 4, 2022.
[34]. T. Lu and T. L. M. Ten Hagen, "A novel kinetic model to describe the ultra-fast triggered release of thermosensitive liposomal drug delivery systems," J. Control. Release, vol. 324, pp. 669–678, 2020.
[35]. P.-C. Chu, H.-Y. Yu, C.-C. Lee, R. Fisher, and H.-L. Liu, "Pulsed-focused ultrasound provides long-term suppression of epileptiform bursts in the kainic acid-induced epilepsy rat model," Neurotherapeutics, 2022.