Review

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Stimulus-responsive liposomes as smart nanoplatforms for drug delivery applications

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Abstract: Liposomes are known to be promising nanoparticles (NPs) for drug delivery applications. Among the different types of self-assembled NPs, liposomes stand out for their non-toxic nature and their possession of dual hydrophilic-hydrophobic domains. The advantages of liposomes include the ability to solubilize hydrophobic drugs, the ability to incorporate different hydrophilic and lipophilic drugs at the same time, lessening the exposure of host organs to potentially toxic drugs and allowing modification of the surface by a variety of different chemical groups. This modification of the surface, or of the individual constituents, may be used to achieve two important goals. First, ligands for active targeting can be attached that are recognized by cognate receptors overexpressed on the target cells of tissues. Second, modification can be used to impart a stimulus-responsive or "smart" character to the liposomes, whereby the cargo is released on demand only when certain internal stimuli (pH, reducing agents,

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specific enzymes) or external stimuli [light, magnetic field, or ultrasound (US)] are present. Here, we review the field of smart liposomes for drug delivery applications.

Keywords: drug delivery; external/internal stimuli; liposomes; nanocarriers; smart stimulus responsive.

1 Introduction

Advances in nanotechnology have made a substantial impact in many different fields and research areas, particularly in biomedicine and pharmaceutics [1–6]. Studies of nanoparticles (NPs) as vehicles for drug and gene delivery and for controlled release have been carried out for the last 20 years [7–10]. Among the many different types of NPs, liposomes are one of the most attractive types for use as drug carriers due to their dual hydrophilic-hydrophobic domains [11]. In 1965, Bangham et al. [12] reported the first "swollen" phospholipid system that formed distinct layers, and during the following years, a novel drug delivery system (DDS) based on liposomes was developed. Liposomes are self-assembled, totally enclosed spherical vesicles composed of non-toxic phospholipids, which are capable of encapsulating both hydrophilic and lipophilic cargomolecules [13].

Liposomes have several special advantages for drug delivery: enhancing the solubility of hydrophobic drugs: the ability to incorporate both hydrophilic and lipophilic drugs at the same time; lessening the exposure of host organs to potentially toxic drugs; and allowing modification of the surface by a variety of different chemical groups [14]. The ability to design smart vehicles that can lead to accumulation of drugs or other therapeutic agents specifically at a diseased site has resulted in the development of the concept of active targeting [15]. Surface modification of liposomes can be carried out by attachment of antibodies (or other ligands that are recognized by over- receptors) for site-specific targeting. Also, chemical moieties can be attached to the surface of the liposomes (or to the constituent building blocks) that will respond to various stimuli. These "smart liposomes" can undergo triggered drug release based on various physiology-dependent properties. The stimuli can be either internal (e.g. enzyme activity, pH changes, or the presence of reducing agents) or they can be external stimuli applied from outside (e.g. temperature, light, magnetic field, or ultrasound (US)) [16]. The release of drug from liposomes based on triggering by external stimuli provides a better accuracy concerning the timing and location of release, and a better control over the delivery and dosage of the drug [17].

Over the last few years, many different FDA-approved liposomes have been introduced for clinical applications, and many others are in different phases of clinical trials. (Table 1).

2 Temperature-responsive liposomes

Temperature plays a critical role in the metabolic activity of cells. The normal mammalian body temperature of 37°C is an ideal temperature for intracellular chemical reactions. Difficulties arise when tissue temperature exceeds the approximate limit of 43–45°C, hyperthermia, as the

Table 1: FDA-approved liposomal drug delivery systems used in clinical application.

Product	Released drug	Treatment	Reference
Doxil	Doxorubicin (DOX)	Kaposi's sarcoma	[18, 19]
		Breast cancer	
Myocet	DOX	Metastatic breast cancer	[20, 21]
Lipodox	DOX	Breast cancer	[22]
		Kaposi's sarcoma	[23]
		Ovarian cancer	
Daunoxome	Daunorubicin	Kaposi's sarcoma	[24, 25]
Marqibo	Vincristine	Acute lymphoblastic leukemia	[26–28]
Amphotec	Amphotericin B	Invasive aspergillosis	[29, 30]
		Serious fungal infections	
Depocyt	Cytarabine	Neoplastic meningitis and lymphomatous meningitis	[31, 32]
Estrasorb	Estrogen	Menopausal therapy	[33]
DepoDur	Morphine sulfate	Pain	[34–36]
Visudyne	Verteporfin	PDT for age-related molecular degeneration	[37, 38]
Epaxal	Inactivated hepatitis A viral strain RG-SB	Vaccine for hepatitis A	[39, 40]

cells will not be able to readily maintain their normal activity [41, 42]. The utilization of mild hyperthermia (HT), a few degrees higher than the physiological temperature, has long been applied together with radiotherapy and chemotherapy in order to boost the efficacy of these treatments with minimal side effects [43, 44]. Temperature-sensitive or thermo-sensitive liposomes (TSLs) have been considered as one of the most efficient types of nanocarriers for site-specific drug delivery applications [45–47].

HT, which can be applied using different modalities, combined with temperature-sensitive liposomes can enhance therapeutic efficiency as follows [48]:

1. Increasing the accumulation of liposomes in the tumor by increasing tumor vascular permeability
2. Controlling the release of therapeutic agents from temperature-triggered liposomes into the tumor vascular and interstitial space
3. Modulating the target cells with enhanced permeability and susceptibility to released drugs
4. Increasing blood flow at the area exposed to heat
5. Exerting direct cytotoxicity to cancer cells while sparing normal cells

The combination of TSL therapy with external HT can be carried out with three different liposome formulations, namely, traditional TSLs (TTSLs); lysolipid-containing TSLs (LTSLs); and polymer-modified TSLs (PTSLs). The design, drug release behavior, mechanisms of thermally triggered release, and the clinical potential of each type have been reviewed by Ta and Porter [48]. Here, we briefly summarize each category and its properties, and highlight recent advances in that particular area.

TTSLs contain traditional phospholipids and undergo a phase transition such as a gel-to-liquid crystallite transition, or a structural transition from lamellar to hexagonal morphology [45, 48]. These types of liposomes were introduced for the first time in 1978 by Yatvin et al. [49, 50]. These authors used dipalmitoyl phosphatidylcholine (DPPC) for the primary lipid with a transition temperature of 41°C, and distearoylphosphatidylcholine was added to DPPC in order to adjust the DPPC transition temperature to the desired value and release the cargo, neomycin. Since then, a number of studies have focused on the preparation of DPPC-based liposomes in combination with other lipids and polyethylene glycol-(PEG)-lipid conjugates in order to enhance the permeability of the liposomal membrane and producing long-circulating (stealth) TTSLs [51–53]. Levachea et al. [52] described a DOX-loaded temperature-sensitive liposome (DOX-TL) composed of a combination of DPPC, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSP), distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide-PEG-2000-ammonium salt] (DSPE-PEG-2000), and cholesterol. This liposomal formulation was triggered in response to local hyperthermia, while it remained stable at physiological temperature. By optimization of the liposomal composition, they successfully improved the stability and inhibited premature drug release in anti-tumor therapy.

LTSLs were first reported by Anyaramabhatla and Needham [54] in 1999 to reduce the phase transition temperature and boost the rapid drug release over a period of tens of seconds. Since then, lysolipid formulations have undergone further development and has shown improved properties in comparison with TTSLs. Studies suggest that the presence of the lysolipid in a relatively low molar percentage in the primary lipid (DPPC) bilayers causes the stabilization of defects in the lipid membrane through the phase transition. The optimized LTSL formulations for rapid drug release and stable liposomal membranes are tailored to have a transition temperature in the range of 39–40°C [48].

Along with the advantages of lysolipids, there is also a drawback consisting of the possibility of the lysolipids leaking from the liposomal shell and degrading the bilayer stability. This led to the idea of synthesizing PTSLs, which has received considerable amount of interest from researchers. The incorporation of polymers can lead to structures that can be either completely or partially degraded, or undergo a phase transition, and disrupt the liposomal membrane in response to heat. These polymers exhibit a lower critical solution temperature (LCST) and an upper critical solution temperature (UCST), below and above which the polymers are soluble, and near these temperatures, the polymers undergo a coil-to-globule transition [45, 48, 55]. Among the different types of temperature-sensitive polymers, poly(N-isopropylacrylamide) (pNIPAAm) has been extensively studied [56, 57]. In a recent study, Pippa et al. [58] synthesized novel temperature-sensitive liposomes by coating DPPC with an end-functionalized $C_{12}H_{25}$-PNIPAM-COOH copolymer. This polymer is temperature-sensitive leading to membrane disruption, and the polymer chains aggregated at temperatures above 32°C. The composition and the molar weight of the PNIPAM chains played an essential role in the thermo-tropic properties of the mixed liposomal membrane. Also, it was shown that by tailoring the DPPC/PNIPAM ratio in the components, drug release from this nanocarrier could be effectively controlled. Turner et al. [59] engineered a thermo-sensitive liposome formulation containing DPPC, soyPC, and cholesterol with optimized molar ratios. Then, the liposome was coated with PEG and dextran, and they compared the

stability and the release behavior of the liposome with these two different coatings. They concluded that dextran and PEG had similar release properties. However, *in vitro* macrophage uptake was greater with dextran. Another example of polymer-modified thermo-sensitive liposomes was described by Guo and Kim [60]. They produced an electrostatic complex between cinnamic acid (CA) and polyethyleneimine (PEI), and the PEI-CA conjugate was immobilized on the surface of an egg phosphatidylcholine (EPC) liposome formulation. The PEI-CA conjugate could be disassembled above its UCST (hindering drug release), and remained assembled below its UCST, which triggered drug release by increasing stress on the liposomal membrane (Figure 1). This PEI-CA conjugate could change its configuration in response to a temperature below or above its UCST thus controlling drug release.

Wang and Kim [26] modified the block co-polymer Pluronic F127 by attaching cinnamoyl groups (CF127) and immobilized it on the surface of EPC liposomes resulting in triggered release of its water-soluble payload in response to a temperature change. The drug release could be triggered by the phase transition of CF127 on the surface of the liposome. When the aqueous solution was heated up, the CF127 underwent micellization and gelation as a result of phase transition, which triggered the drug release from the liposomal membrane. Another approach for producing polymer-modified thermo-sensitive liposomes was recently described as the so-called "polymer-caged nanobins" (PCNs). In this study, a hydrogel network was integrated over the surface of a liposomal carrier. Cholesterol-terminated poly(acrylic acid)(chol-PAAc) chains were immobilized into the bilayer membrane of the drug-loaded liposome, and then, chol-PAAc chains were crosslinked with telechelic diamine linkers. This gel-like three-dimensional network of polymers was thermo-sensitive, which induced drug release from the liposomal core [61].

In addition to the three above-mentioned extensively studied categories (TTSLs, LTSLs, and PTSLs), other novel liposomal formulations have been reported. "Nanohybrid liposomal cerasomes" (NHLC) are one of these formulations [62–65]. NHLC are liposomal bilayers with an inorganic silicate framework on the surface. This system is biologically stable. However, slow drug release from this carrier can be considered to be one of its drawbacks. Recently, Liang et al. [66] developed a stable NHLC formulation, thermo-sensitive cerasome (HTSC), that displayed rapid thermo-sensitive drug release upon exposure to high-intensity focused ultrasound (HIFU). This system consisted of four types of lipids, each of which played a distinct role in the formulation, including N-[N-(3-triethoxysilyl)propylsuccinamoyl]-dihexadecylamine (CFL), DPPC, mono C17 lipid (MSPC), and DSPE-PEG-2000. Different molar ratios of CFL to DPPC were explored to enhance serum stability and thermal sensitivity. This formulation was prepared using a thin-film hydration method inside and a self-assembly process leading to sol-gel reaction. In this system, the presence of DSPE-PEG-2000 induced rapid drug release. Figure 2A illustrates the formation of the aforementioned nanosystem, its drug release behavior, and a comparison to conventional low temperature-sensitive liposomes (LTSLs).

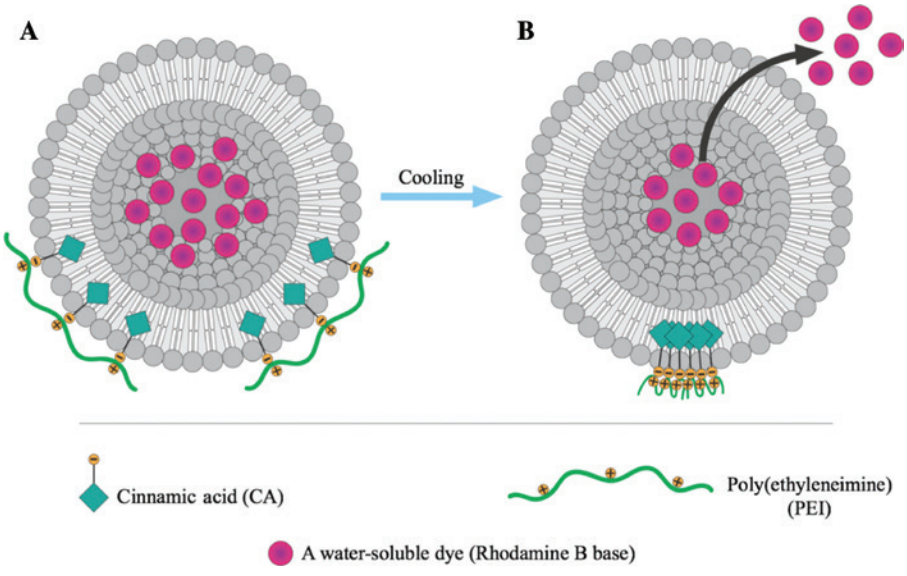

Figure 1: Schematic of temperature-dependent behavior of liposome-conjugating PEI-CA (A) above UCST and (B) below UCST.

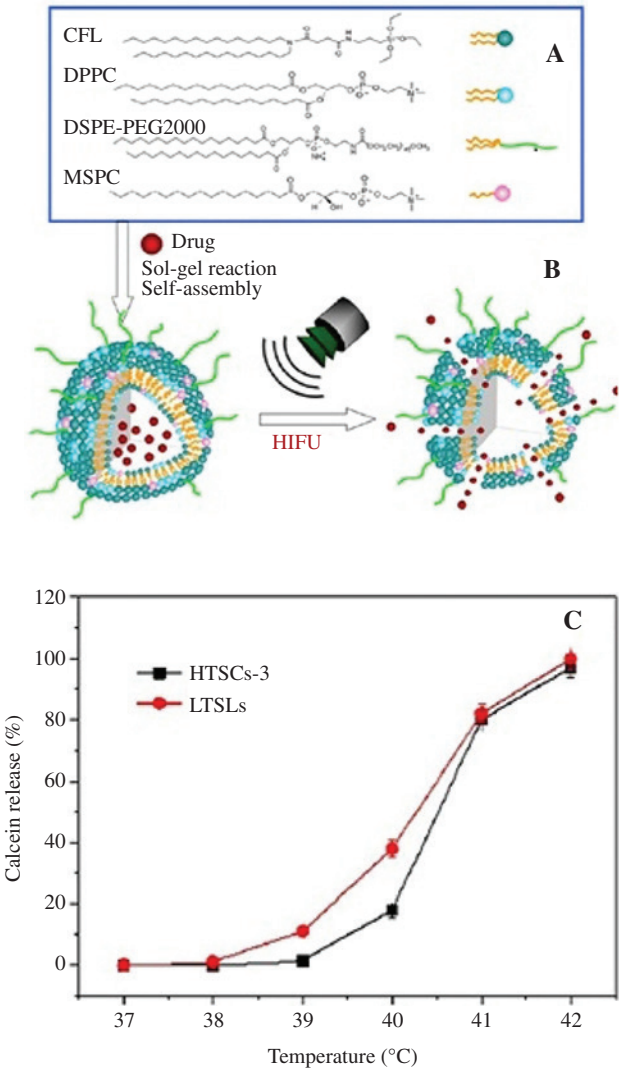

Figure 2: Ultrasound-sensitive drug-loaded liposomal cerasome. (A) Schematic of the formation of drug-loaded nanohybrid liposomal cerasome and its drug release on exposing the system to HIFU [66]. The release behavior of one of the synthesized HTSC formulations (HTSCs-3) compared to the component lipids of conventional low temperature-sensitive liposomes (LTSLs) is shown in (C). It was concluded that below 41°C, LTSLs released calcein (used as a model drug) more rapidly than HTSCs; however, above 41°C, LTSLs and HTSCs-3 exhibited similar release profiles. Accordingly, HTSCs-3 showed a more narrow temperature-responsive range, which was better for drug release in the hyperthermia range. This formulation overcame one of the disadvantages of temperature-sensitive liposomes, *viz* variable drug delivery efficiency due to heterogeneous heat distribution in the tumor tissue after mild hyperthermia (that occurs due to variations in tumor vascularity). (B) Release behavior of one of the HTSCs' formulations compared to LTSLs. Reprinted with permission from Ref. [66], copyright 2015, American Chemical Society.

Another approach that can be applied for further enhancing of the therapeutic efficiency and bioavailability of TSLs is active targeting using cell-specific ligands such as antibodies, folate, and peptides, which can be attached to the surface of TSLs. Some degree of targeting can also be achieved by incorporating cationic lipids into the bilayer [44, 67–69]. Kono et al. [67] synthesized thermo-sensitive liposomes with target specificity. Different types of PEGylated liposomes were functionalized with thermo-sensitive poly (2-2-ethoxy) ethoxyethyl vinyl ether) chains and conjugated to a monoclonal antibody, trastuzumab (Herceptin) that recognizes the HER2 receptor, which is overexpressed on some breast cancers. The liposomes were loaded with indocyanine green for near-infrared fluorescence imaging. Owing to the specific interaction between the antibody and its target cells, the liposomes accumulated efficiently at tumor sites.

3 Light-responsive liposomes

Among the diverse external stimuli, the use of light as a triggering agent for smart DDSs has been extensively reviewed in the literature [4, 5]. Light is particularly attractive as a wide variety of parameters, such as wavelength, duration, the intensity of the beam, and beam diameter, can be tailored to achieve the desired release profile and tissue penetration. Furthermore, non-invasive light activation can be exerted with high temporal and spatial control [70]. Electromagnetic light wavelengths below 650 nm cannot penetrate deeply through tissue (>1 cm) because of scattering and absorption by endogenous chromophores (like water, lipids, and hemoglobin) [71]; thus, although UV light can trigger a lot of chemical reactions, it can be employed as a triggering agent only for superficial treatments applied to the skin and mucosa [72]. The main strategy to obtain a deeper light penetration is the use of near-infrared (NIR) light within the wavelength range of 650–1000 nm, which also causes less damage to living cells [73].

Liposomes are among the most studied types of light-responsive NPs. The key element in the light-responsive NPs is the necessity for a chromophore (a chemical moiety that can capture light energy) [4]. Many mechanisms have been developed to induce light-triggered release from NPs, such as photo-crosslinking [74], photo-un-crosslinking [75], photochemical hydrophobicity switch [76], and photo-induced cleavage of chemical bonds [77]. Mechanisms used in light-sensitive liposomes can be categorized into three groups, photo-crosslinking, photochemical triggering, and photo-isomerization [78]. Each mechanism works on the basis of a light-triggered change in the chemical structure of a specific molecule. Some important

photo-sensitive chemical groups are azobenzene and spiropyran (that undergo a photo-isomerization transition), and coumarin (that undergoes a photo-crosslinking reaction) [79].

3.1 Photo-crosslinking (photo-polymerization)

Although photo-crosslinking or photo-polymerization has been used as a means for formation of NPs, this same mechanism can also be employed as a means to trigger drug release from liposomes. Photo-polymerization causes short- or long-lived pores to occur in the liposome membrane by polymerizing double bonds in components in the hydrophobic part of the liposome bilayer, leading to shrinkage of the bilayer, and consequent drug release (Figure 3) [80]. Recent studies have also employed photosensitizers in the liposome structure to increase the sensitivity and to shift the wavelength of light absorption into the visible region [81]. Yavlovich et al. [82] prepared photo-triggerable liposomes from photo-polymerizable diacetylene phospholipid and DPPC, which released calcein (a fluorescent dye entrapped in liposome) upon treatment with UV light (254 nm).

3.2 Photochemical activation

Many mechanisms can lead to the disturbance of structured assembly of the lipidic components of the liposome bilayer and the consequent release of its contents: photosensitization-induced oxidation (photodynamic), triggering with "photo-acid generators", and photo-deprotection of fusogenic lipids [73, 83]. An example of the use of a photosensitizer in photochemical triggering is the activation of plasmenylcholine by photosensitizers activated by NIR light. Photosensitizers including octabutoxyphthalocyanine, Zn-phthalocyanine, and bacteria-chlorophyll-α, which absorb light between 630 and 820 nm, can lead to the photo-triggering of liposomes and the release of payload [83].

3.3 Photo-isomerization

Another approach to develop light-responsive liposomes is to use polymers that have been modified by attaching chromophores that undergo conformational changes upon light irradiation [84]. Lipids can be modified with light-responsive chromophores such as azobenzene, spirooxazine, stilbene, fulgide, or spiropyran groups. All these contain a double bond, which can undergo trans-to-cis isomerization in their structure (Figure 4A). Azobenzene is among the most attractive chromophores due to its favorable properties, including high stability, bright color, low flammability, and reversible and fast isomerization [87]. The mechanism involves switching from nonpolar and more stable trans-isomer, to the more polar cis-isomer upon excitation with visible, UV, or even NIR wavelengths leading to drug release [85, 86, 88] (Figure 4B and C).

The most attractive feature of photo-isomerization is its reversibility, i.e. the conversion of cis back to trans is a relaxation back to the more stable state and can be achieved by irradiation with longer wavelengths of light or by thermal relaxation [2]. Many studies have investigated azobenzene-modified liposomes; for example, Ishii et al. introduced azobenzene into the amphiphilic region of the 1,2-dioleoyl-sn-glycero-3-phosphocholineliposomal membrane in order to change the membrane permeability by light irradiation [89]. Yao et al. [87] reported a NIR light-responsive azobenzene-liposome carrier, loaded with DOX. It was found that >90 wt% of DOX was released under 7.8 W/m^2 power density (Figure 4C).

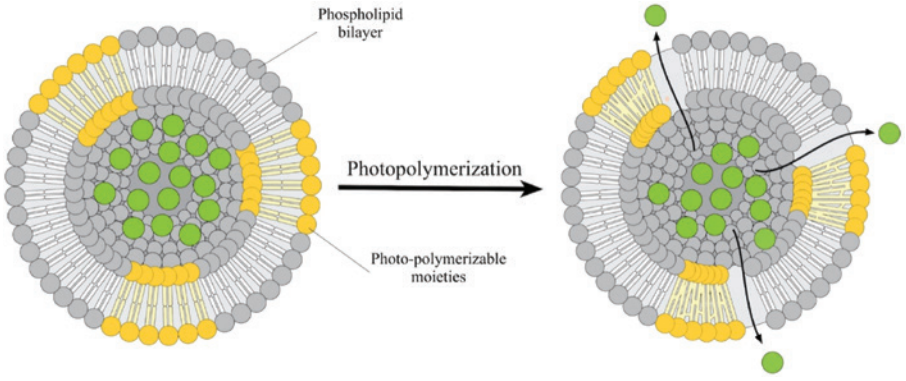

Figure 3: Schematic of light-activated polymerization of liposomes, leading to the release of cargos.

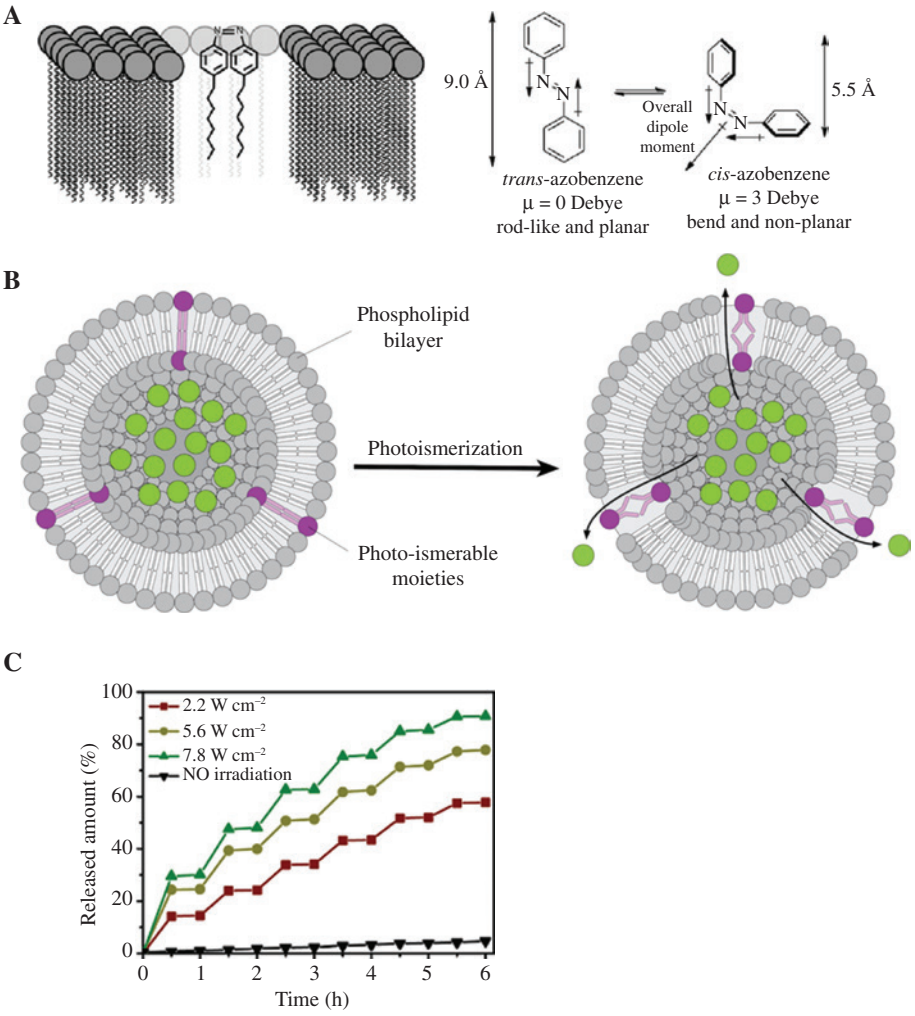

Figure 4: Light-sensitive liposomes via cis-trans isomerization of azobenzene. (A) Schematic of a liposomal membrane equipped with azobenzene moieties (left), and the polarity alterations during the reversible cis-trans isomerization of azobenzene (right) [85] (open access). (B) Schematic of photo-isomerization mechanism that occurred in liposomal carriers. (C) Drug release curves under 980-nm irradiation (Release obtained in buffer and under the irradiation duration time of 30 min). Reprinted with permission from Ref. [86], copyright 2016, John Wiley & Sons, Inc.

3.4 Photo-induced thermo-responsive release

In contrast with conventional bulk gold metal salts, gold nanostructures (NPs, nanoshells, nanorods, nanocages, etc.) can absorb light in the NIR region and in the visible region (five times higher absorption coefficients than common photo-absorbing dyes) [90]. The absorption occurs due to the surface plasmons (quasi-particles of plasma oscillation), whereby the conductance electrons possess a high resonance with certain electromagnetic frequencies [91]. The photo-absorption by gold nanostructures increases the temperature by forming a "heated electron gas", which loses its energy rapidly (within 1 ps) by heat exchange with the nanostructure lattice. Thereby, the surrounding medium is heated locally within a time scale of 100 ps [92]. This thermal property can be employed to trigger release of the drugs entrapped in the liposomes (Figure 5) [93]. Moreover gold NPs can be used on their own in laser-induced hyperthermia-based cancer treatment, in which tumor tissue is targeted by Au-NPs to kill the cancer cells [94, 95].

Wu et al. [96] prepared DPPC liposomes loaded with hollow gold NPs and 6-carboxyfluorescein (a fluorescent dye used as a soluble model drug). Here, hollow gold NPs had a maximum absorption at 820 nm, and the maximum drug release occurred at 4.3 W/cm^2 power density. Recently, Lajunen et al. [97] described a liposomal DDS loaded with gold NPs prepared in nanostar and nanorod shapes. The release profile of the calcein payload was investigated as a function of temperature (Figure 6).

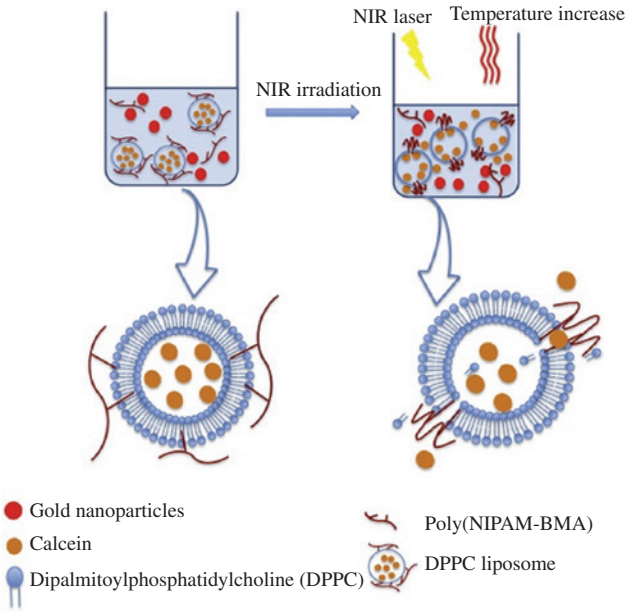

Figure 5: Schematic of gold NPs being excited by NIR radiation leading to drug release from thermosensitive liposomes. Reprinted with permission from Ref. [93], copyright 2015, Elsevier.

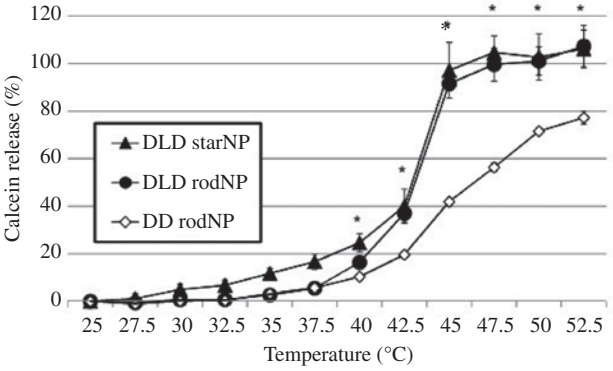

Figure 6: Curves indicating calcein release profiles (DLD, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1-stearoyl-2-hydroxy-snglycero-3-phosphocholine,1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol) and DD, 1,2-distearoylsn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine). Reprinted with permission from Ref. [97], copyright 2015, Elsevier.

4 pH-sensitive liposomes

Although significant developments have been achieved in addressing the challenges related to liposomal drug delivery, there are still some major problems [98]. One of the most important challenges is the ability of the delivery system to selectively enhance the bioavailability of the drugs at the target site, as well as to maintain its stability in the blood circulation until it reaches its destination. Currently, one of the most common strategies to overcome the aforementioned problem is "pH-sensitive liposomes". This strategy is frequently used to target cancer as relatively low pH is one of the most common features of solid tumors. Moreover, the release of liposomal contents inside the acidic compartments of cells (endosomes or lysosomes) can also be achieved. The principle mechanism of these NPs is the destabilization of the structure under acidic conditions, which, in turn, leads to the release of their contents. In other words, the acidification of the surrounding medium induces selective destabilization of the liposomal membrane [98, 99].

However, the aforementioned strategy has two major limitations. First, in the case of tumor therapy, the acidic sections of tumors are located remotely from the microvasculature, as that is where hypoxia is most pronounced leading to accumulation of lactic acid due to the cellular metabolism switching to glycolysis (Warburg effect). This remoteness from the blood supply makes it difficult for IV-injected liposomes to efficiently accumulate. Second, as the tumor pH range rarely reaches lower than pH 6.5, it is technically difficult to fabricate engineered liposomes that are capable of efficiently responding to such a small pH change (~1 pH unit) [98, 100].

The structure of the pH-sensitive liposomes generally consists of a neutral lipid, which is usually a phosphatidylamine derivative such as dioleoylphosphatidyl-ethanolamine (DOPE), dioleoylphosphatidyl choline or N-succinyl-DOPE, and a weakly acidic amphiphile, such as cholesteryl hemisuccinate (CHEMS) [101–103]. The negatively charged group of the phospholipid undergoes destabilization in an acidic environment, leading to enhanced liposomal fusion with the cell membrane (in tumors) or with the endosomal membrane (inside cancer cells) and, ultimately, the release of its contents [98, 104]. Researchers have been trying to introduce novel lipids as a replacement for DOPE. Several approaches such as the combination of cationic/anionic lipids, a lipid diolein with CHEMS, and a formulation containing eggPC combined with Tween-80 have also been reported [105, 106]. These new formulations have shown much better pH-responsive characteristics compared with DOPE liposomes.

Liposome recognition by opsonins (naturally occurring serum proteins designed to remove foreign bodies from the circulation) and, subsequently, their endocytosis and clearance by the reticulo-endothelial system (RES) are other hindrances to the implementation of the liposomal drug delivery [107]. Moreover, the liposomal carrier and its contents can be totally degraded by various enzymes after its delivery to the lysosomes after endocytosis occurs into target cells (Figure 7) [108]. Therefore, efficient strategies

must be developed to design liposomes, which can release their contents into the cytosol (so the drugs can reach the nucleus, which is often the final site of action) before they are degraded in the lysosomes. One useful technique applied for reducing the RES uptake and prolonging the circulation time is the incorporation of PEG-lipid conjugates into the liposomal bilayer [109, 110]. However, the problem with this approach is that PEGylation may interfere with the membrane fusion of the liposome and may even cause membrane destabilization [111]. One suggested solution to this problem was to develop liposomes that were capable of losing their coating polymer before they reached their target sites. This approach resulted in the introduction of liposomes with a cleavable linker between their coating polymer chain and the hydrophobic part of the liposome bilayer. Through surface modification, the stability and cellular uptake efficiency of liposomes can be enhanced; for example, via exploitation of novel materials such as maleimide [112, 113].

One of the new strategies of designing pH-sensitive liposomes is the modification of the liposome surface with pH-labile polymers [114–116]. Accordingly, Yuba et al. [117]. designed pH-labile polymers using dextran derivatives containing 3-methylglutaraldehyde residues (MGLu-Dex). The surface modification of egg yolk phosphatidylcholine (EYPC) liposomes with MGLu-Dex was reported to show significant destabilization in weakly acidic environments (Figure 7). In another study, Zong et al. [118] reported a controlled release liposome platform using polydopamine (PDA)-coated liposomes as pH-sensitive carriers. They

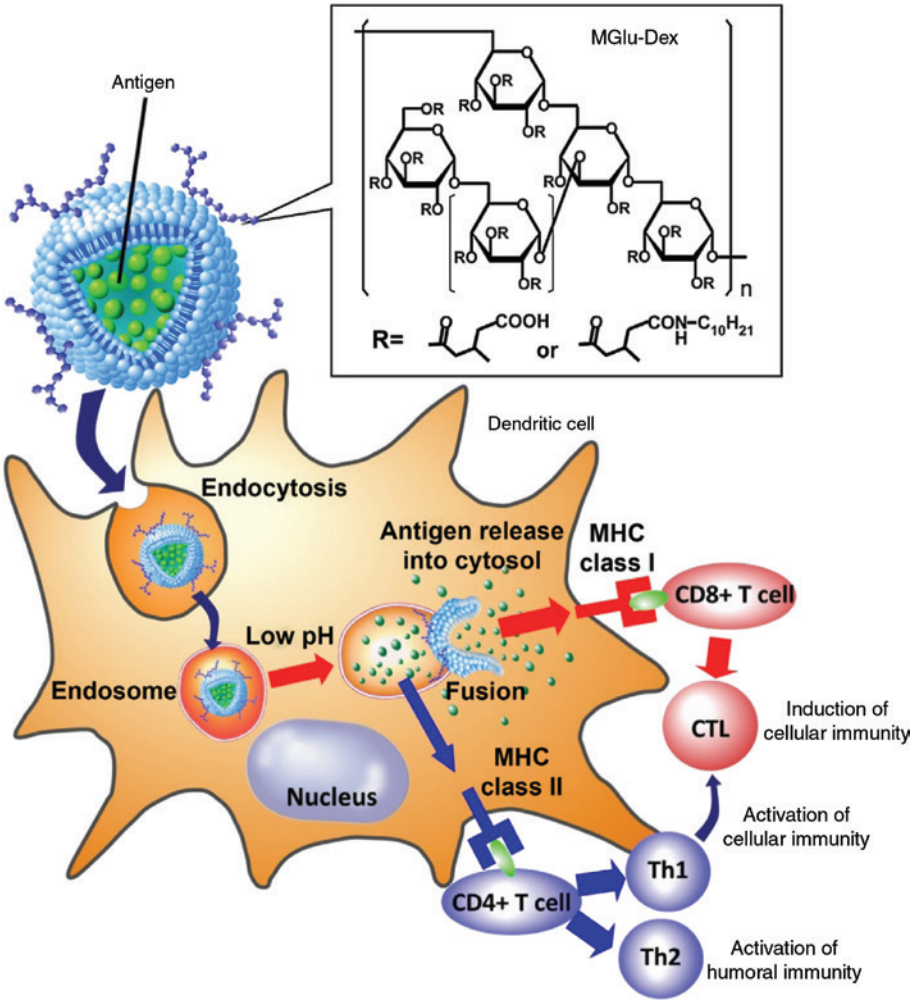

Figure 7: Design of MGlu-Dex-modified liposomes as a vaccine for induction of antigen-specific immunity. MGlu-Dex-modified liposomes are taken up by dendritic cells (DC) via endocytosis and trapped in endosome. The weakly acidic DC cytosol induce the formation antigen-specific cytotoxic T lymphocytes (CTL) via presentation by MHC class I, resulting in induction of cellular immunity (Th1 response). Antigen molecules in the endosomes undergo presentation by MHC class II and induce antigen-specific Th2 cells that lead to induction of humoral immunity. Reprinted with permission from Ref. [117], copyright 2014, Elsevier.

used a chemotherapeutic agent, 5-fluorouracil (5-FU), as the liposomal cargo. It was demonstrated that 5-FU-loaded pH-sensitive liposomes showed improved performance compared to free drugs at tumor pH (pH 6.87).

Another important class of pH-sensitive liposomal delivery systems is attached to target-specific ligands, such as folate and transferrin, or to cell-penetrating peptides, such as TAT [100]. These ligands are capable of recognizing and binding to specific receptors overexpressed on the target cells. This method is known as "active targeting" in contrast with "passive targeting" in which liposomes accumulate at target sites merely according to their size (enhanced permeability and retention effect) [100, 119]. The combination of surface modification to target folate receptors (FR) (overexpressed on many different types of solid tumors), together with a pH-responsive liposome strategy, improved the performance of FR-targeted anticancer drugs as the FR receptor-mediated endocytosis leads to endosomal localization. Other important ligands that are used for surface modification of liposomes include monoclonal antibodies that are against antigens, such as H-2K^k (expressed in different types of tumor cell), E-selectin (on activated vascular endothelial cells), p-glycoproteins (on endothelial cells), CD-19 (on B-lymphoma cells), CD (on T-leukemia cells), and so forth. Immuno-liposomes, which use antibodies as their surface modification on the pH-sensitive liposomes, are also well investigated. Immunoglobulins (IG) of the IgG class and their derivatives are extensively exploited as targeting moieties that can be incorporated to the surface of liposomes with no undesired effects on the liposomal integrity [120–125].

Although the main focus of most studies carried out on pH-responsive liposomes has been the pH-controlled disturbance of the membrane structure, there are studies on different mechanisms based on internal acidification of liposomes [126, 127]. More recently, there have been several attempts performed to develop pH-labile liposomes for addressing multidrug resistance of cancer cells. Liu et al. prepared novel pH-labile liposomes loaded with DOX using a NH_4HCO_3 gradient method. The bicarbonate ion (encapsulated within the liposome structure) reacted in acidic environments to produce copious quantities of CO_2 gas, which subsequently disturbed the liposome membrane and allowed drug release (Figure 8) [128, 129].

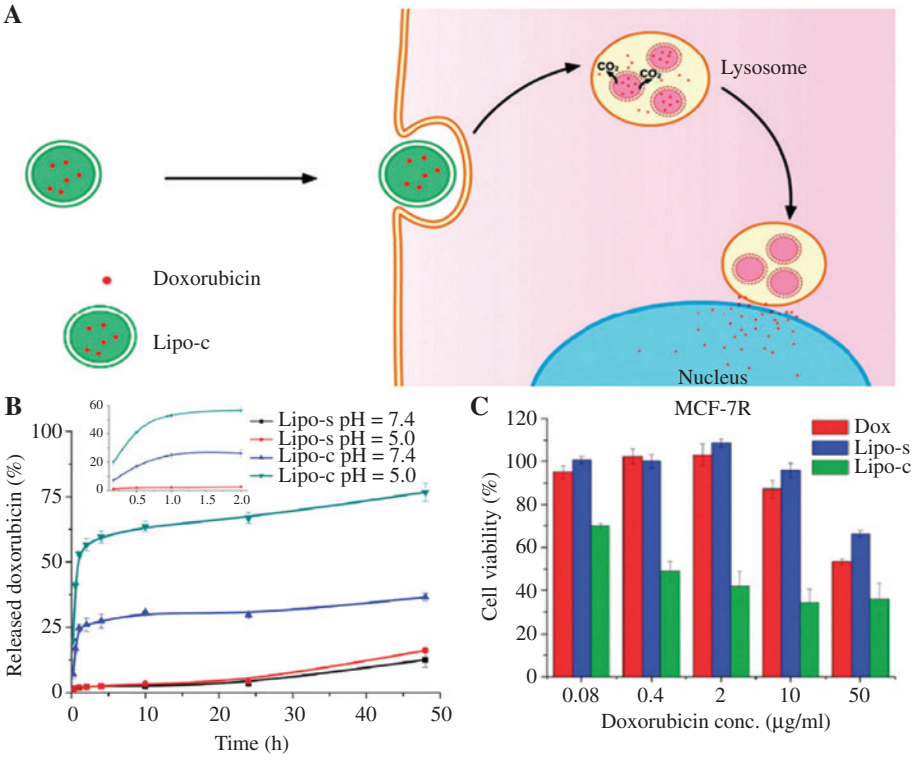

Figure 8: Gas generating-based pH-labile liposome. (A) A novel DOX-encapsulated liposome with NH_4HCO_3 will produce CO_2 in an acidic environment leading to drug release. (B) Quantitative DOX release from pH-sensitive liposome (Lipo-c) and normal liposome (Lipo-s). (C) The resistant MCF-7 cell viability after treatment with DOX-encapsulated liposomes. Reprinted with permission from Ref. [128], copyright 2012, Royal Society of Chemistry.

Table 2: Several examples of pH-labile liposomes reported in literature for anti-cancer therapy.

Liposome formulation	Preparation method	pH-sensitive moiety	Encapsulated cargo	Target site/cell line	Encapsulation/ release efficiency (%)	Size (nm)	Bioassay	Reference
DOPE/HSPE/CHEMS/CHOL/ $mPEG_{2000}$–DSPE(4:2:2:2:0.3)			DOX	B lymphoma cells	95/–	120	*In vitro*	[141]
PEG-HZ-PE		TAT peptide	TAT peptides	H9C2 rat embryonic cardiomyocytes, LLC tumors			*In vitro* and *in vivo*	[142]
DOPE/CHEMS/DSPE-PEG		Unsaturated phosphatidylethanolamine	Cisplatin	A549 (lung cancer) A431 (cervix cancer) GLC4 (lung cancer) Ehrlich solid tumor	26.3/– 23	110 121, 130	*In vitro* and *in vivo*	[143–145]
PEG/PE,TATp		Cell-penetrating TAT peptide	DOX	B16-F10,HeLa and MCF-7 cells	–	120	*In vitro*	[146]
Fplate-poly(2-ethyl-2-oxazoline)-DSPE		FPEOz-DSPE	DOX	Human ovarian cancer cell SKOV3	91/45	100–150	*In vitro*	[147]
DOPE/DSPG/DSPE-PEG(7:3:0.53)			Methotrexate	Rat femoral artery	2.51/37	143	*In vitro* and *in vivo*	[148]
PC/DDAB/CHEMS/ Tween-80/Folate-PE-PEG (25:25:49:1:0.1)	A procedure based on polycarbonate membrane extrusion	OAlc-containing liposomes targeted to the FR	Cytosine-*b*-D-arabinofuranoside	KB human oral cancer cells	15/33,83 (dependent on Tween-80 concentration)		*In vitro*	[149]
HSPC/CHEM/PEG/ diethylenetriaminepentaacetic acid-modified phosphatidylethanolamine			Calcein		–/>20	88–102	*In vitro*	[150]
PEtOz-CHEMS	Lipid film hydration method		DOX	A375 cells	96/90	100–120	*In vitro* and *in vivo*	[151]
PE:Chol:OA (3:2:3)	Thin-film dispersion method		Docetaxel		–/86.9	277	*In vivo*	[152]
DOPE:CHEMS:PDP-PEG-DOPE (6:4:0.1)	Reverse-phase evaporation vesicle method	EGFR dioleylphosphatidylethanolamine (DOPE)	Gemcitabine	A549 (lung cancer)	67/–	146	*In vivo*	[153]
HHG2C18-L and PEGHG2C18-L	Film dispersion method	Zwitterionic oligopeptide lipids hexahydrobenzoic amide	Temsirolimus (CCI-779)	A498 (renal carcinoma) Renca (murine renal carcinoma)	93.76/<1(for *in vitro*)	104.5	*In vitro* and *in vivo*	[154]
S100PC:Chol:mPEG-Hz-Chol (90:10:3)		Hydrazone	Paclitaxel	MCF7 (breast cancer)	92.2/65.8	132.6	*In vitro*	[155]

DOPE, dioleoylphosphatidylethanolamine; CHEMS, cholesteryl hemisuccinate; Chol, cholesterol; DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; HSPC, hydrogenated soy phosphatidylcholine; PC, phosphatidylcholines; PE, pphosphatidylethanolamine; DSPG, dipalmitoylsuccinylglycerol; PEG, poly ethylene glycole; DDAB, dimethyldioctadecylammonium bromide; PEG-HZ-PE, PEG and PE being conjugated with the lowered pH-degradable hydrazone bond; HHG2C18, 1,5-dioctadecyl-lglutamyl 2-histidylhexahydrobenzoic acid; HS, hydrogenated soy; PEtOz, poly(2-ethyl-2-oxazoline).

Generally, pH-sensitive liposomes have demonstrated a variety of applications including (1) delivery systems for chemotherapy, (2) pH-sensitive immunoliposomes, (3) tumor diagnostic tools, and (4) biological macromolecule (vaccine/DNA/gene/oligonucleotide) delivery systems [104, 130–140]. Table 2 summarizes the applications of anticancer drugs delivered via pH-responsive liposomes.

5 Ultrasound responsive

US can be simply described as acoustic waves with frequencies higher than 20 kHz, which is higher than the audible range of human hearing [156]. The common medical applications of US include imaging, tissue ablation, kidney stone disruption, physiotherapy, and so forth [157]. However, the original idea of using US as a method for drug delivery dates back to the era when biochemists began using US to rupture biological cell membranes to remove the cell contents before purification [158]. One of the advantages of using US for drug delivery is that it can be focused from outside to any organ almost regardless of depth, which makes it reasonably suitable for the targeted delivery of anticancer drugs/genes to tumors located in the pancreas, brain, as well as any other organ such as the liver [159].

The role of US in drug delivery nanocarriers such as liposomes is to rupture the structure of the phospholipid bilayer. As the pulses of the US waves propagate through tissue, some physical phenomena take place: cavitation, hyperthermia, and acoustic streaming [160]. It is currently understood that cavitation is the main factor that governs the response of liposomes and other lipid-based nanocarriers subjected to US [161]. Gas bubbles (which may be present already) or which can form as the pressure drops below the vapor pressure of the surrounding medium, will undergo rapid oscillations, i.e. expansion and contraction, as the pulses of US arrive. These oscillations in gas bubbles are called cavitation bubbles. Depending on the frequency and amplitude of the US waves as well as the size and properties of the bubbles, there are two types of cavitation: internal and stable [157, 160] (Figure 9). At lower US intensities, stable cavitation occurs, while at higher US intensities, internal cavitation takes place. Internal cavitation can eventually lead to bursting of the bubbles, and hence, drug release occurs [162]. Studies on delivering doxorubicin (DOX) encapsulated in micelles suggested that low-frequency US would cause more efficient drug release than high-frequency US [163]. The mechanism of the drug release is due to the internal cavitation of gas bubbles occurring near these micelles [160] (Figure 10A). Cavitation, in liposomes, which have an additional layer of phospholipids compared to micelles, either occurs near the liposomes (like micelles) or can occur inside their lipid bilayers [160] (Figure 10B). Low-frequency US waves also show better results in rupturing liposomes [164]. It has also been shown that using low-frequency US on liposomes did not alter the chemical properties of the encapsulated drug or destroy its activity [165].

Microbubbles (MB), were originally designed as a contrast agent for US imaging. However, they are also able to function in drug delivery applications [2]. MBs consist of a gas-filled core that can contain air, nitrogen, or perfluorocarbons (PFC), which is surrounded by a layer/layers of lipids, proteins, or polymers [2]. PFC compounds loaded into MBs have a pronounced ability to dissolve oxygen. Accordingly, Chang et al. investigated the delivery of oxygen along with a fluorescent dye [1,10-dioctadecyl-3,3,30,30-tetramethylindocarbocyanine iodide] (DiI), a model drug, loaded into the liposomal MBs. Using US and fluorescence imaging in *ex vivo* tissue models, it was found that multifunctional MBs could provide simultaneous controlled delivery of oxygen and therapeutic agents [166]. Generally speaking, MBs, themselves, have a limited drug loading capacity. This limitation requires using highly active drugs [167]. Although some drugs such

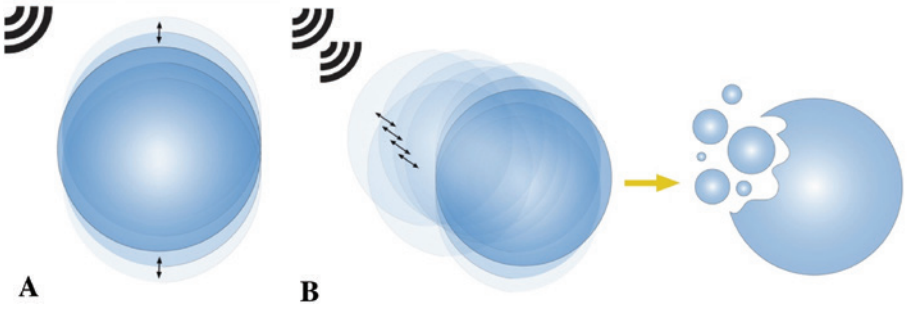

Figure 9: Stable and internal cavitation. (A) Stable cavitation: bubble oscillations due to low power US pulses, which are non-resonant. (B) Internal cavitation: high-power pulses will lead to amplified resonance and finally collapse of the bubble.

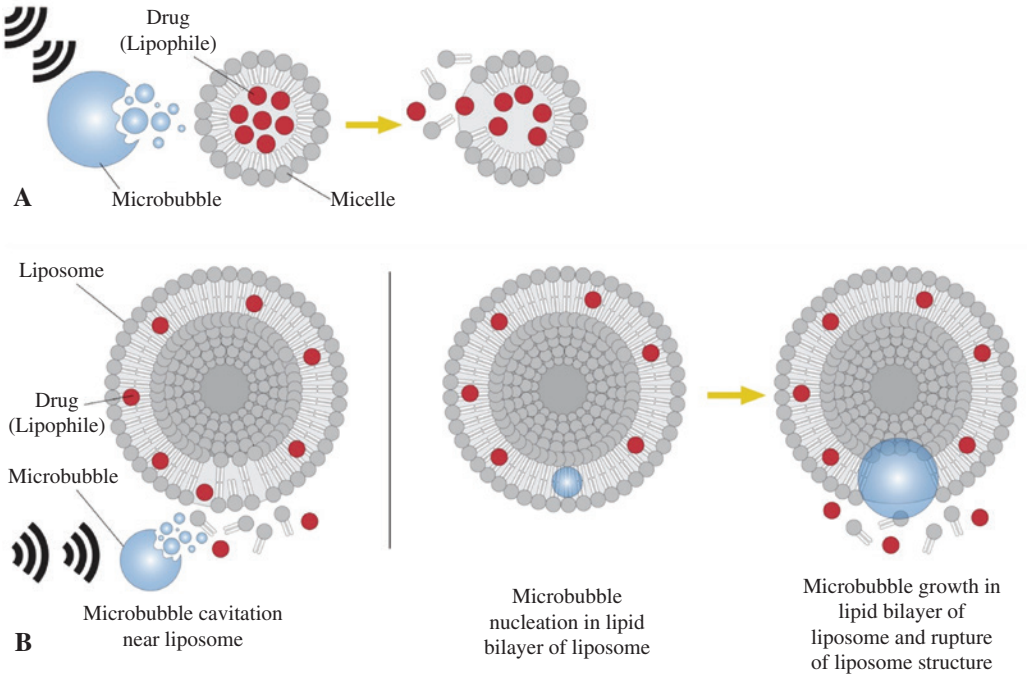

Figure 10: Proposed mechanism for (A) cavitation effect on micelle rupture, (B) liposome collapse.

as DOX can be loaded onto the coated lipid bilayer of MBs via electrostatic attraction and hydrophobic forces (only for lipophilic drugs), liposome-encapsulated drugs that are conjugated or attached to external MBs can have a higher loading efficiency [168]. Yu et al. performed studies on combining liposomes with MB for delivery of DOX utilizing US. As demonstrated in Figure 11, this method led to increased loading of the drugs, thus, achieving improved results. Their results showed that it was possible for a MB to carry about 1600 liposomes. Furthermore, low-pressure US pulses resulted in more efficient drug release [168].

Recent advancements in the field of US-responsive liposomal DDSs have focused on designing the so-called "sonosensitive" materials to be employed in liposomes to achieve better results. These efforts include a study conducted by Evjen et al. who found promising results using liposomes composed of 1,2 distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE) and liposomes comprised of dioleoylphosphatidylethanolamine (DOPE) [169, 170]. *In vitro* study of DSPE showed about 70% release of DOX within 6 min of US exposure, which was a sevenfold improvement compared to standard PEGylated liposomal DOX [170]. DOPE *in vitro* showed even better results: releasing 95% of DOX from liposomes in 6 min of 40-kHz US exposure; a 35% increase compared with using DSPE, and a ninefold increase compared to standard PEGylated liposomes [169]. Other than using the aforementioned sonosensitive agents to modify the phospholipid bilayer,

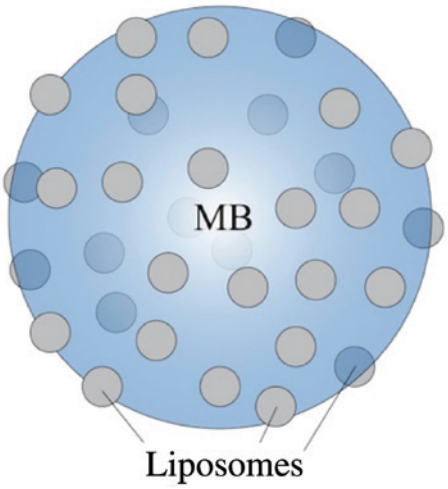

Figure 11: Potential ability of microbubbles to carry a large number of liposomes and, hence, increasing the drug loading capacity (see text).

it is also possible to use bile salts (BS) to make vesicles with higher sensitivity to an US stimulus. It has been reported that BSs destabilize the structure of the phospholipid bilayer [171]. Recently, Mujoo et al. attempted to use BSs (e.g. cholate, chenodeoxycholate, ursodeoxycholate, glycocholate, and taurocholate) to make improved US-sensitive phospholipid bilayers. They also demonstrated significant responses to low-frequency US, whereas non-significant responses were obtained for high-frequency

US. They also found that liposomes made of taurocholate and DOPE showed less sensitivity to high-frequency US than liposomes containing only DOPE. It was speculated that this phenomenon was because of a preferred shape arising from the combination of taurocholate and DOPE in the phospholipid bilayer [172].

Sonoporation is another effect that can be exerted by US action on nanocarriers, which is defined as the formation of temporary pores in the cellular membrane. The generation of these pores is an opportunity for the penetration of drugs into the cells especially for delivery of drugs into the brain where the blood brain barrier (BBB) is the most important barrier against drug uptake. The underlying mechanism for such pore formation is mainly due to cavitation and also hyperthermia associated with MB US activation [161, 173]. For example, Lin et al. studied cationic liposomes (CLs) for the delivery of DOX to brain tumors using focused US. The idea of using cationic liposomes originated from the general characteristic of tumor cells, i.e. their more negatively charged surfaces. Their investigation on glioma, a common brain tumor, showed promising results where tumors became smaller, and animal survival was increased [174].

As mentioned previously, MBs generally can be used for the delivery of highly active drugs. However, siRNA, miRNA, and plasmid DNA also have the potential to produce a biological effect at comparatively low doses. This non-viral gene delivery can also be combined with US. Grayburn et al. applied this method with cationic liposomes for diabetes treatment using RIP 3.1, an insulin-specific promoter, to trigger the expression of gene NeuroD. Their histological studies on diabetic rats showed the regeneration of pancreatic islets employing this technique [167].

In spite of many studies on US for drug delivery, it is still difficult to be quantitatively precise concerning US parameters. This is mostly because different US methods use different frequencies and materials. Moreover, the fact that cavitation is also accompanied by hyperthermia makes it difficult to study the effect of cavitation alone on lipid-based nanocarriers. One method to study the cavitation effects more specifically is using different frequencies and investigating the effects of temperature and/or US pulses on drug release [160].

6 Magneto responsive

In recent years, lipid-based NPs that also contain magnetic substances, the so-called magnetic/magneto-liposomes (MLs) have been developed for the diagnosis and therapy of miscellaneous diseases. As an example, metallic ions and magnetic NPs (MNPs) can be bound to, or encapsulated into, liposomes during the synthetic processes. Metallic ions such as Gd (III) have been used as a contrast agent (CA) for magnetic resonance imaging (MRI). In comparison with metallic ions, MNPs cannot only be used as CAs but also have other applications such as magnetic targeting, therapeutic hyperthermia, and magnetically triggered drug release [175]. Passive and active targeting of magnetic liposomes are potentially applicable in delivering other therapeutic agents at the same time. This ability can lead to the design of multimodal systems for theranostic purposes.

The combination of various methods such as hyperthermia and photodynamic therapy (PDT) is an interesting strategy to enhance therapeutic efficiency, and ultramagnetic liposomes can be employed for this purpose. In one study, the bilayers of liposomes that were highly loaded with MNPs in the hydrophilic core and also contained a photosensitizer (FOSCAN™) in the hydrophobic region were used for cancer therapy. Stimulation with an alternating magnetic field raised the temperature of the MNPs. Besides, magnetic NPs also played a role as MRI CAs. Laser excitation activated the photosensitizer, and the surrounding oxygen was changed into a reactive form (singlet oxygen). Also, the fluorescence emission of the photosensitizer could be used for imaging. The coupling of magnetic hyperthermia and PDT potentiated the tumor destruction caused by the singlet oxygen. The mechanism of this process was triggering apoptotic pathways that led to more complete cancer cell and tumor regression *in vivo*. This approach could avoid surgical damage and preserve the surrounding normal tissues [176].

Magnetic fluid-loaded liposomes (MFLs) have been reported to address the problem of inefficient chemotherapy of malignant tumors in the brain and central nervous system. In one study, labeled PEGylated liposomes loaded with maghemite crystals could pass the BBB. To further investigate this approach, glioblastoma cells were implanted intracerebrally in nude mice. Then, MFLs were intravenously injected. Because of the vasculature permeability induced by a magnetic field gradient applied to the heads of the mice, the tumor was targeted both by EPR and magnetic targeting. Thus, the concentration of the MFLs was selectively increased in the malignant area. Also, a 7T small animal MRI system was used to monitor the process at the same time [177].

An anti-EGFR antibody conjugated to magnetic liposomes was used as an active targeting system, for

co-delivery of drugs and genes. In this platform, DOX was loaded into mesoporous silica magnetic NPs coated by a liposomal bilayer. Mesoporous silica not only facilitated high drug loading (98% efficiency) but also enhanced the interaction of water molecules with the magnetic core, which enhanced the MRI contrast. Here, Plk1 siRNA was first treated with protamine to form a complex; afterward, the complex was incorporated into the liposomal system by the ammonium bicarbonate gradient technique. pH-sensitive drug release was shown at acidic pH values. These multifunctional theranostic particles were tested as image-guided therapy on BxPC3 pancreatic cancer cells [178].

The increased temperature resulting from magnetic-stimulated MLs can damage the healthy surrounding tissue. To prevent this side effect, ~5-nm nitrodopa-palmityl stabilized magnetic NPs were embedded into the liposome bilayers. Magnetic stimulation increased the temperature to the melting point of the liposome bilayers, which caused a change in the permeability. Controlled release and optimized drug loading were the most significant achievement [179]. Another research demonstrated that simultaneous encapsulation of SPIONs and methylene blue dye into the lipid bilayer-coated mesoporous silica NPs (MSNs) could function as a remote smart-triggered DDS. MSNs provided higher encapsulation efficiency and allowed interaction of the SPIONs with lipid bilayers, and the effect of alternating magnetic force on the melting temperature of lipid bilayers made the gates stimulus responsive [180]. Elsewhere, magnetite NPs were deposited on the surface of melamine formaldehyde particles that were coated by polyelectrolyte. The core was dissolved to form a microcapsule structure. The layer-by-layer assembly led to a covering of the temperature-responsive lipid bilayers on the surface of the microcapsules. Under a magnetic stimulus, the microcapsule could trap and release the dye [181]. Recently, Salvatore et al. reported a new type of MLs that contained a fluorescent hydrophilic drug combined with a single-stranded oligonucleotide (ON) conjugated to a cholesteryl unit of the liposome membrane. Two types of MNPs were employed in this platform. A hydrophobic MNP was located in the liposome bilayer, and an ON-decorated hydrophilic gold core-shell MNP was connected to the single-stranded ON on the surface. Controlled and sequential release could be obtained by the frequency changes in an alternating magnetic field (AMF). Five minutes of 3.22-kHz AMF caused the release of a model drug, whereas 15 min of 6.22-kHz AMF released the DNA because the temperature increased to the melting point of the DNA (Figure 12) [182].

MRI is a non-invasive diagnostic tool, where the excitation of the nuclear spin leads to an energy transition, and the time for the relaxation of the nuclei can be detected by MRI [183]. In recent years, DDSs have been suggested to simultaneously serve as drug carriers and CAs for enhancing MRI images. This aim could be achieved by increasing longitudinal relaxivity. The study of the abnormal muscle contraction or investigating brain physiology is facilitated by MRI. Fluctuations in cellular calcium (Ca^{2+}) can be used in an intelligent CA for MRI. This probe has features such as specific local tissue targeting, improvement in retention time, and modifying and amplifying the MRI signals. To this end, a formulation of a novel amphiphilic ligand in the liposome structures that contained a Gd(III) complex was reported as a CA. Ca^{2+} binding to magnetic liposomes changed the coordination of the Gd-chelate. In fact, Ca^{2} increased hydration and reduced the local motion of the Gd(III) complex, and the increase in relaxivity could be detected even at low-magnetic field values. Therefore, this type of smart CA triggered by molecules or ions involved in neuronal signaling can help neuroscience studies for the better understanding of brain function [184]. Aptamer-conjugated thermosensitive liposomes encapsulating Gd-DTPA were employed as an MRI probe. These

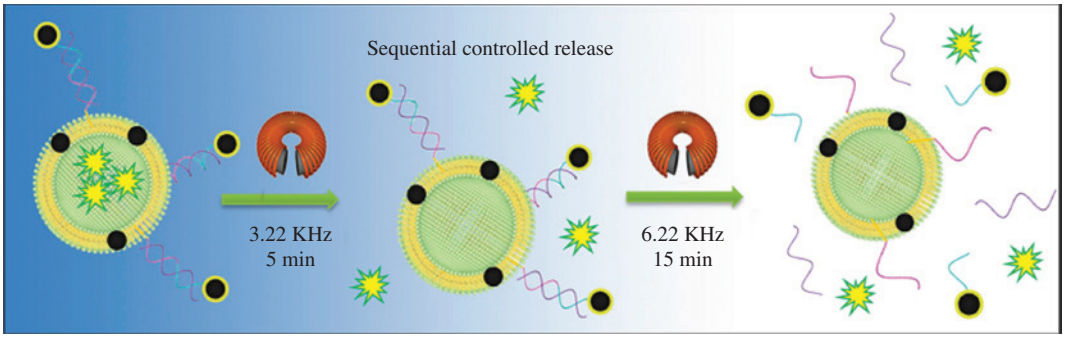

Figure 12: Schematic illustration of sequential controlled release of dual MNP-equipped liposomes. Reprinted with permission from Ref. [182], copyright 2016, American Chemical Society.

biocompatible MLs enhanced cellular uptake, due to active targeting whereby the Gd CA was released at 42°C via mild hyperthermia. Such a CA delivery system could improve early cancer diagnosis [185]. Another study by Zhang et al. showed that the encapsulation of Mn^{2+} in liposomal NPs not only could be monitored by MRI but also facilitated high encapsulation of As_2O_3 in the liposomes. Actually, the reaction of Mn^{2+} and As_2O_3 produced a complex structure (Mn-As complex). The complex formation and deformation affected the darkness and brightness of the MRI image contrast. Mn^{2+} alone was a dark T_2-weighted CA, whereas the Mn-As complex was a bright T_1-weighted CA. This convertible MRI platform could provide drug release inside glioblastoma cells, and furthermore, a high dosage of As overcame the temozolomide resistance of glioblastoma [186].

Carbon nanostructures are promising materials and can be combined with MLs. In one study, buckyball (fullerene C_{60}) was utilized for surface decoration of magnetic NPs and also for the adsorption of hydrophobic drugs or fluorescent dyes by a π-π stacking mechanism. Folate-targeted thermosensitive liposomes encapsulated PEG-functionalized C_{60}-Fe_3O_4 nanocomposites and docetaxel (DTX) as a multifunctional system. Herein, the fullerene hybrid system was shown to increase the temperature after radio-frequency radiation. Fullerenes could be used for radiofrequency-triggered release of DTX and with increased accumulation of the fullerenes and DTX in tumor tissues. Histological studies showed that the coupling of radiofrequency and magnetic field targeting of this multifunctional system caused cell necrosis, lysis, and fragmentation [187].

Recently, a new type, "nanorobots", was introduced where the combination of liposomes, carbon nanohorns (CNH), and magnetic iron NPs were investigated as a nanotransporter. This structure allowed monitoring of cancerous cells even at the single-cell level. The liposome structure encapsulated the fluorescein di-β-D-galactopyranoside (FDG) as a quenched non-fluorescent agent that could be activated by β-galactosidase, which was conjugated with a "teddy bear"-shape, made of avidin-biotin-polyethylenimine (PEI)-MAG-functionalized-CNH-ox hybrid. These hybrids were investigated as a novel theranostic platform (Figure 13D). Confocal microscopy

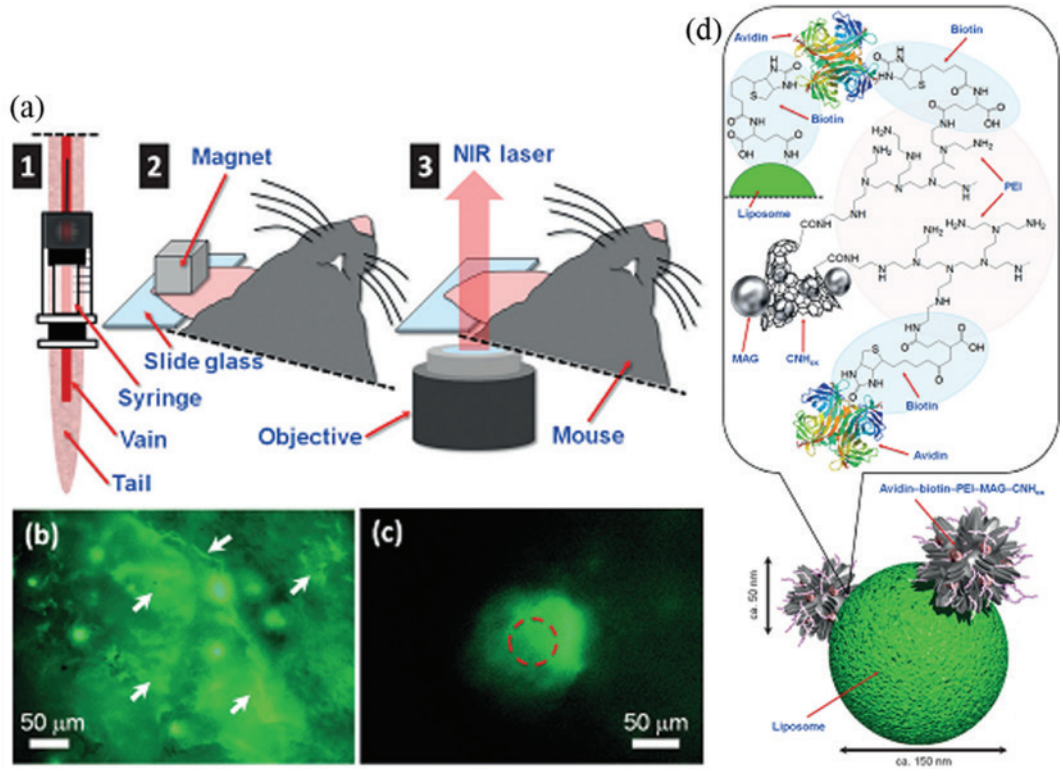

Figure 13: *In vivo* remote control of enzymatic reactions using nanotransporters. (A) Schematic image of the experiment. (1): injection of nanotransporters, (2): Nanotransporters accumulated by a magnet, (3): Manipulation and observation of physicochemical aspects of nanotransporters with NIR radiation. (B) Accumulation of nanotransporters in the vessels by magnetic field. (C) *In vivo* β-Gal reaction observed in the blood vessel of a living mouse. (D) Nanotransporter structure. Reprinted with permission from Ref. [188], copyright 2016, John Wiley & Sons, Inc.

showed the magnetic field effect to improve transfection yield in HeLa cells *in vitro* (magnetotransfection). Cytotoxicity tests confirmed the biocompatibility of the nanohybrids in the presence of the magnetic field. Finally, the nanotransporter was applied for the remote control of enzymatic reactions *in vivo* (Figure 13). To illustrate this ability, FDG encapsulated nanotransporters injected into transgenic mice that expressed human β-galactosidase in the whole body. Simultaneous magnetic field and laser induction were used to trap the nanotranporters in the vessels of the mouse ear, and release the FDG. Because of the β-Gal enzymatic reaction, the green fluorescence of fluorescein was produced by hydrolysis of FDG and could be directly observed *in vivo* [188].

7 Other stimulus-responsive smart liposomal carriers

7.1 Matrix metalloprotease 2 (MMP2)

Novel multifunctional DDSs for cancer targeting that are responsive to matrix metalloprotease 2 (MMP2), which is often upregulated in a tumor environment, have been developed. In a recent study, a liposomal nanocarrier was designed comprised of (PEG (providing elongated blood circulation and preventing non-specific interactions) on the liposomal surface, which was also conjugated to an antinucleosome monoclonal antibody (mAb2C5). Because of the EPR phenomenon, this liposomal nanocarrier accumulated in the location of the tumor (due to the nanocarrier size) and also exhibited active targeting by the mAb2C5. Therefore, in the microenvironment of the tumor, the MMP2-sensitive linker between PEG and lipid was cleaved because of up-regulated extracellular MMP2; thus, the protective long-chain PEG was removed. This led to the exposure of the hidden surface-functionalized cell-penetrating peptides (TATp), which facilitated intracellular delivery of the drugs. Therefore, targeted and enhanced cell internalization of the nanocarriers was obtained [189].

In another study, copolymers based on the self-assembly of PEG-phosphoethanolamine (PEG-pp-PE) demonstrated MMP2-sensitive drug delivery to tumor cells, and the drug efflux mediated by P-glycoprotein (P-gp) was prevented. In this research, different homologous of PEG-pp-PE were studied. This investigation proved that the total structure of PEG-peptide-lipid was crucial for the inhibition of P-gp, and the equilibrium between its hydrophilic and lipophilic parts was important. Here, PEG2k-pp-PE gave a higher inhibition of P-gp. This copolymer exhibited a promising tumor-targeted drug delivery, which was connected with the enhancement in plasma membrane fluidity and the inhibition of the activity of P-gp ATPase [190].

7.2 Redox

A study by Noyhouzer et al. demonstrated the controlled payload release of a ferrocene-modified phospholipid unilamellar liposome as a drug delivery vehicle by a redox-active mechanism. This takes advantage of the fact that the redox potential is higher inside cancer cells due to a higher concentration of glutathione. Here, the exposure of the ferrocene groups on the surface of the vesicle were shown, thus, providing for triggering the redox reaction. Therein, the results of flow cytometry evaluating the drug release in HeLa cells indicated a 200-times stronger signal for the cells treated with redox active vesicles. This implicated an efficient redox-sensitive delivery and provided specificity to the cancer cells [191].

8 Dual-sensitive liposomes

Stimuli-responsive characteristics are among the efficient approaches to improve the precision of drug delivery; thus, to date, diverse stimuli-responsive systems have been designed [192–194]. Liposomes can discharge their cargos in response to temperature, pH, light, and redox signals. Normally, the stimulus results in alterations in the structure of the lipid, as well as the destabilization and leakage of the liposome contents. In this section, we will cover liposomes that respond to a combination of these different stimuli [195, 196]. The most common format of dual-responsive liposomes is an “AND” logic gate where both stimuli must be present at the same time to get a drug release.

8.1 pH/temperature responsive

Combined temperature-responsive and pH-sensitive liposomes have been investigated as they show controlled release when exposed to increased temperature and an acidic surrounding milieu [68, 134]; thus, the design of the nanocarriers responsive to both temperature and pH changes provides new opportunities for controlled drug delivery [197, 198]. In one study, dual-stimuli responsive liposomes reacting to both pH and temperature were

fabricated with biocompatible hyperbranched poly (glycidol) (HPG) containing pH-labile succinyl moieties and temperature-responsive oligo (ethylene glycol) (OEG) moieties. This nanoplatform switched from hydrophilic to hydrophobic in response to pH and temperature changes of the surrounding environment, and the NPs were destabilized [197]. In another study, Chen et al. synthesized a liposomal gel formulation, sensitive to alterations in both temperature and pH. This platform was used for vaginal administration of arctigenin employing a cleavable methoxy polyethylene glycol 2000-hydrazonecholesteryl hemisuccinate (mPEG-Hz-CHEMS). Thus, high stability was found at neutral pH, but in acidic conditions (pH 5), the platform was destabilized via bond cleavage. The results showed that the vaginal gel loaded with arctigenin was an effective formulation for the treatment of vaginal candidiasis with less toxicity [198]. In another study, Kono et al. synthesized hyperbranched poly (glycidol) containing N-isopropylamide (NIPAM), as a thermo-responsive moiety, and succinylate groups as the pH-labile component. In response to a decrease in pH and an increase in temperature, the polymer NP altered from hydrophilic to hydrophobic [199]. Such polymers have been also incorporated onto stable EYPC liposomes to generate dual sensitive liposomes and could deliver payloads into the cytosol of target cells under an acidic environment and local heating [200]. Furthermore, Wu et al. demonstrated that an MSN as the drug-encapsulating core and a copolymer-lipid layer comprised of phospholipids and poly(N-isopropylacrylamide-methacrylic acid-octadecyl acrylate) as the dual-responsive shell could allow the delivery of a drug such as DOX. Here, changes in temperature and pH could each trigger the release of drugs in response to more acidic and higher temperature of cancerous cells, respectively [201].

8.2 Temperature/ultrasound responsive

Thermo-sensitive liposomes (TSLs) experience a phase alteration when they are heated, and this phenomenon makes them permeable inducing the release of their cargo [202]. Conventional TSLs are activated between a temperature range of 42°C and 45°C, and release their cargo over 30 min, while LTSLs discharge their drugs at a temperature range of 39°C to 40°C in a few seconds [203].

High-intensity focused HIFU is able to ablate tumors by employing rather long and continuous exposures to produce high temperatures for tumor thermal ablation [204]. Dromi et al. have combined pulsed HIFU with LTSLs to elevate the local delivery of DOX into tumors. The results showed the improvement of the antitumor effects of the drugs [205]. Elsewhere, Chen et al. designed a curcumin-encapsulated liposome MB gel comprised of N-cholesteryl hemisuccinate-O-sulfate chitosan (NCHOSC). This liposomal MB had a high loading efficiency for curcumin. The temperature-responsive CS/GP gel containing liposomal MBs assumed a gel format body temperature where the initial release of curcumin induced by US was found to be 85%. In Figure 14A, a schematic image of the process and the release diagram are shown. The results implied the fact that the double responsive curcumin-loaded liposomal MB gel served as a potential ultrasound and temperature dual-responsive DDS [206]. Oerlemans et al. developed fluorescent liposomes (FCLs) that mediated ablation with the aid of MR-HIFU for the treatment of non-palpable breast

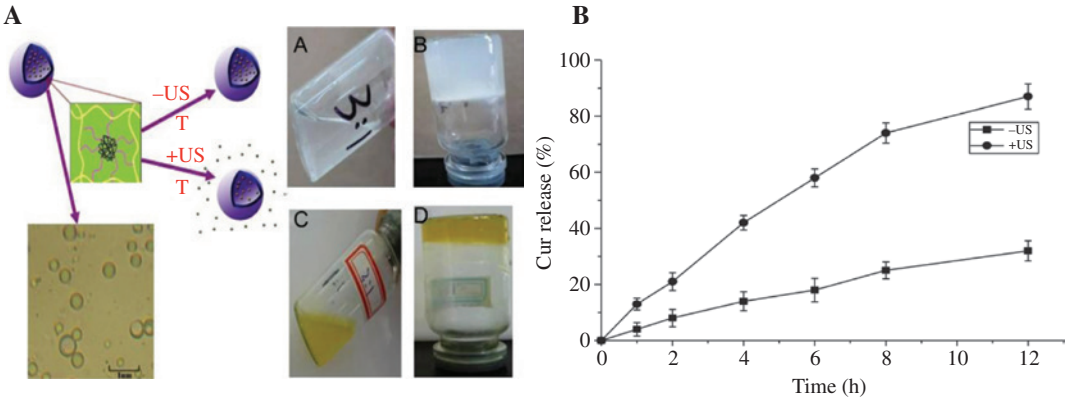

Figure 14: (A) Schematic illustration of Cur-LM-G and the external morphology of the blank liposome microbubble gel is shown at the middle: (A) under the temperature of gelation, (B) gelation process, (C) the formed Cur-LM-G under the temperature of gelation, and (D) gelation. (B) The percentage of curcumin that is released from Cur-LM-G in the presence and without the presence of US. Reprinted with permission from Ref. [206], copyright 2013, Elsevier.

lesions. FCLs could liberate their fluorescent contents after 30 s of exposure to MR-HIFU. After exposure and release of the contents, the treated lesions could be imaged by fluorescence excited by UV light. PEG and cholesterol were included in the liposome to provide more stability and elongated circulation time. Through introducing thermosensitive phospholipids like 1,2-dipalmitoyl-sn-glycero-3-phosphocholine into the liposomes, MR-HIFU-mediated fluorescein release from the liposome could be accomplished [207].

8.3 pH/redox responsive

The combination of pH and redox is another category of dual-response liposomes. It is known that the pH of the tumor microenvironment is between 6 and 7, which is lower than physiological pH. It also becomes more acidic (e.g. pH between 5 and 6) inside the intracellular endocytic vesicles [208]. Additionally, glutathione (GSH) has a significantly higher concentration inside cells, making it a promising option for smart intracellular drug delivery. Recently, Zhang et al. developed a cleavable polymerized liposome (CPL) for the delivery of pharmaceutical agents. A gallate-derived group with three propargyl moieties was joined to palmitoyl oleoyl phosphoethanolamine (POPE). To create large unilamellar vesicles, the mentioned anionic lipid was formulated with other lipids including palmitoyl oleoyl phosphatidyl choline. Employing the Cu(I)-catalyzed click reaction between the propargyl moieties and the azides in the crosslinker resulted in the polymerization of the unilamellar vesicles. The polymerized liposomes equipped with a disulfide or ketal group in the crosslinker could be depolymerized and discharge their payload through the addition of a reducing thiol or under acidic conditions, respectively [209]. Elsewhere, a PEGylated nano-sized polymeric lipid vesicle (PPLV) loaded with DOX exhibited dual pH and reduction responsiveness. The system enabled efficient antitumor drug delivery via triggered drug release, as well as enhancing tumor cellular internalization. The PPLVs were reported to have good uptake by tumor cells under acidic conditions. On the other hand, an accelerated DOX release at pH 5 as well as with 10 mM of GSH proved its promising potential [210]. In a similar study, another dual-responsive DDS containing folate-PEG-coated polymeric lipid vesicles (FPPLVs) was constructed showing an enhanced DOX release profile under acidic conditions in comparison to neutral pH values due to the loss of PEG in acidic conditions, which, in turn, made it easy for tumor cells to take up the NPs. Fluorescence microscopy of HeLa cells also showed that disrupting the FPPLV structure in response to 2–10 mM of intracellular GSH levels triggered drug release in tumor cells [211].

Xu et al. designed acid/redox dual responsive liposomes, comprised of soy phosphatidylcholine (SPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), and a synthetic functional lipid, 2-[2-(2-carboxylcyclohexylformamido)-3,12-dioxy-1-(1H-imidazolyl-4)-7,8-dithio-4,11-diazapentadecylamide]-glutaric acid ditetradecanoldiester (HH-SS-E2C14). HH-SS-E2C14 contained histidine, an amino acid moiety, and acid-cleavable hexahydrobenzoic (HHB) amide, as a hydrophilic block, and two tetradecyl alkane chains as a hydrophobic block. A disulfide bond was integrated into the structure as a redox-labile linkage between the two blocks. When this formulation was administered intravenously, it had a negative charge, but after the EPR enabled the accumulation in tumors, the surface charge became positive due to the interaction with cell membranes, which were negatively charged. Subsequently, after endocytosis, the imidazole group was protonated and promoted the proton influx into the endocytic vesicle followed by an increase in osmotic pressure and rupture of the endo-lysosomes, allowing endo-lysosomal escape of the cargo [212].

8.4 Other dual responsive liposomes

8.4.1 pH/enzyme

Zhang et al. created a dual stimuli-responsive liposome, responsive to pH and esterase for the delivery of camptothecin and siRNA for the treatment of cancer. This dual CPT-PCB (poly carboxy betaine)/siPIK1 lipoplex preparation showed a high capacity for loading of CPT and could boost the serum stability of the liposomes and provide controlled release of CPT and siRNA, due to the protonation of PCB in endosome/lysosomes, and esterase and pH sensitivity of the CPT-PCB prodrug. This system was reported to be a promising delivery platform for cancer therapy and co-delivery of CPT and siPIK1 [213].

8.4.2 Dual redox

Moreover, a co-assembly system comprised of block copolymers containing diselenide and polymeric lipid could show dual redox responsiveness because it could be disrupted when exposed to either allow the concentration of hydrogen peroxide (as an oxidant) or glutathione (as a reductant). In the presence of 0.05 mM of GSH or 0.1% H_2O_2, most of the co-assembly system was disrupted. Also,

the results illustrated that hydrophobic interactions provided the driving force of the co-assembly [214].

8.4.3 Redox/ultrasound

In 2013, Nahire et al. showed that polymer-coated echogenic lipid NPs could release their content via redox triggering and in response to diagnostic frequency US. As a result, a 3-MHz US combined with a reducing agent increased the drug release up to 96%. Such lipid NPs were stable in oxidizing environments and released their content in the reducing environment of the cytosol. The rate of drug release was boosted by simultaneous application of redox trigger and US [215].

9 Conclusion

Liposomes have long been one of the most studied types of drug delivery nanosystems. In addition to the other advantages described in some detail above, another overriding reason lies in their remarkably low toxicity. Widespread concern about possible hazardous effects of diverse nanostructures such as carbon nanotubes, fullerenes, noble metal nanostructures, various inorganic NPs, quantum dots, and so forth has led to the establishment of a brand new area of toxicology called "nanotoxicology". In contrast to many of these nanostructures, liposomes are principally composed of naturally occurring lipids that are naturally found as constituents of cell membranes that compose all the cells of our bodies. The body is well used to dealing with the basic components of liposomes, so they can be regarded as the ultimate in biocompatibility and biodegradability. This is probably why there are more liposomal preparations that have gained regulatory approval for medical applications, than any other class of NPs. Now that liposomes have almost progressed to being the "standard of care", the road is open for researchers to improve upon them by active targeting strategies, and by engineering various stimulus-responsive and smart characteristics.

Smart modification of liposome is an opportunity to impart a stimulus-responsive moiety to the structure. Herein, encapsulated cargos can be released through activating the stimuli-responsive part followed by alterations in the structure of liposome, e.g. conformations, or bond cleavage and the structural destabilization of the carrier, thus, leading to the leakage of the cargos. These alterations can be triggered on-demand and with highly precise control via internal stimuli (pH, reducing agents, specific enzymes) or external stimuli (light, magnetic field, or US). In this regard, smart stimuli-responsive liposome vehicles are opening new horizons for drug/gene delivery applications and innovative therapies for various diseases and disorders, especially in clinical evaluations and exploitations.

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