Review

Light-Responsive and Dual-Targeting Liposomes: From Mechanisms to Targeting Strategies

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Review

Light-Responsive and Dual-Targeting Liposomes: from Mechanisms to Targeting Strategies

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Abstract: Over recent years, nanocarriers have played an ever-increasing role in clinical and biomedical applications owing to their unique physicochemical properties and surface functionalities. Lately, much effort has been directed towards the development of smart, stimuli-responsive nanocarriers that are capable of releasing their cargos in response to specific stimulus. These intelligent-responsive nanocarriers can be further surface-functionalized so as to achieve active tumor targeting in a sequential manner, which can be simply modulated by the stimuli. By applying this methodological approach, these intelligent-responsive nanocarriers can be directed to different target-specific organs, tissues or cells, and exhibit on-demand controlled drug release that may enhance therapeutic effectiveness and reduce systemic toxicity. Light, an external stimulus, is one of the most promising triggers for use in nanomedicine to stimulate on-demand drug release from nanocarriers. Light-triggered drug release can be achieved by light irradiation at different wavelengths, either in UV, visible or even NIR region, depending on the photophysical properties of the photo-responsive molecule embedded in the nanocarrier system, the structural characteristics and material composition of the nanocarrier system. In this review, we highlighted the emerging functional role of light in nanocarriers, with emphasis on light-responsive liposomes and dual-targeted stimuli-responsive liposomes. Moreover, we provided the up-to-date phototriggered targeting strategies and mechanisms of light-triggered drug release from liposomes and NIR-responsive nanocarriers. Lastly, we addressed the current challenges, advances, and future perspectives for the deployment of light-responsive liposomes in targeted drug delivery and therapy.

Keywords: smart nanocarriers; light-responsive liposomes; dual-targeted stimuli-responsive liposomes; phototriggered targeting strategies; light-triggering mechanisms; NIR-responsive nanocarriers; current challenges; future perspectives

1. Introduction

1.1. Liposomes as Drug Nanocarriers

Nanocarriers were first discovered in the early 1960s, when scientists proposed the application of liposomes for drug delivery [1]. Since then, many nanocarrier systems have been developed and approved for marketing by the U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMA). Nanocarriers have been extensively used in drug delivery owing to their exceptional physicochemical properties, such as nanometric particle size, surface charge, high entrapment efficiency and drug loading capacity [1,2]. Nanocarriers used in cancer treatment have received particular attention from global researchers, since most conventional chemotherapeutic drugs cause systemic toxicity resulting from their poor stability in biological systems, non-selectivity and non-

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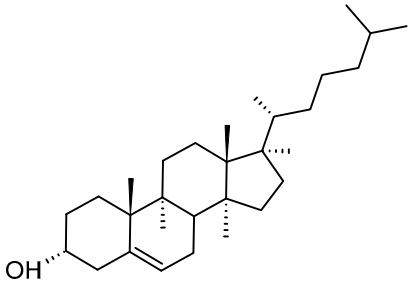
specificity toward cells expressing the targeted receptors [2]. The first evidence on feasibility and effective use of nanocarriers in cancer treatment was reported in 1976 by Langer *et al.* [3], who prepared the first sustained-release, long-circulating poly(ethylene glycol)-poly(lactic acid-ethanolic acid) (PEG-PLEA) nanoparticles, which in the later approved by the FDA as the first nanomedicine for therapeutic use in cancer treatment. Generally, nanocarriers are categorized into two main classes: organic and inorganic nanocarriers [4,5]. Organic nanocarriers include nanoemulsions (10-1000 nm), nanosuspensions (<1 μm), nanoliposomes (50-450 nm), polymeric nanoparticles (10 nm to 1 μm), solid-lipid nanoparticles (10-1000 nm), and nanodendrimers (15-200 nm); while inorganic nanocarriers include gold nanoparticles (5-400 nm), silver nanoparticles (1-100 nm), mesoporous silica nanoparticles (30-300 nm), and superparamagnetic iron oxide nanoparticles (100 nm to 5 μm). These tumor-targeted, nano-sized drug delivery systems were developed primarily to reduce the systemic toxicity of chemotherapeutic drugs through encapsulation into nanocarrier systems, which allowed to achieve site-specific delivery with improved passive and active drug targeting (i.e., disease-specific targeted therapeutics). Of all these nanocarriers, liposomes are very promising drug delivery systems with advantages of being non-toxic, biocompatible and biodegradable [1]. Liposomes were first discovered by Bangham *et al.* [6] in 1964. They discovered how membrane molecules interact with water to form unique structural forms, which were described as swollen phospholipid systems [6]. Briefly, liposomes are defined as vesicular systems consisting of one or more concentric spheres of phospholipid bilayers separated by aqueous or buffer compartments [6,7]. When phospholipids are dispersed in an aqueous medium like water or buffer, hydration of phospholipid polar heads results in a heterogeneous mixture of spherical structures, generally referred to as vesicles, most of which contain multiple phospholipid bilayers forming concentric spherical shells [6,7]. Those were the liposomes first reported by Bangham *et al.* [6,7], nowadays referred to as multilamellar large vesicles (MLVs). Sonication of these lipid dispersions results in size reduction of these liposomes to vesicles containing only a single bilayer with diameters ranging from 20-100 nm, later referred to as small unilamellar vesicles (SUVs) [8]. Large unilamellar vesicles (LUVs, 100-1000 nm) are intermediate in size between MLVs (>700 nm) and SUVs [8]. The main components of liposomes are phospholipids and cholesterol, which are naturally-occurring substances [9]. Phospholipids are amphiphilic molecules with hydrophobic non-polar tails and hydrophilic polar heads. These amphiphilic molecules spontaneously organize into liposomes in an aqueous or buffer environment, driven by hydrophobic interactions and other intermolecular interactions [1,9]. The proper choice of phospholipid is important to achieve the desired effects. Table 1 shows the most commonly used phospholipids in the preparation of liposomes (Data extracted from Sigma-Aldrich and Avanti Polar Lipids database). Figure 1 shows the classification of liposomes according to their structures, sizes, compositions, and preparation methods.

Table 1. Lipids used for the preparation of liposomes (Data extracted from Sigma-Aldrich and Avanti Polar Lipids database).

Lipid name & CAS No.	Synonym	Molecular formula	Chemical structure
Neutral			
Cholesterol (CAS No.: 57-88-5)	---	$C_{27}H_{46}O$	
Anionic			

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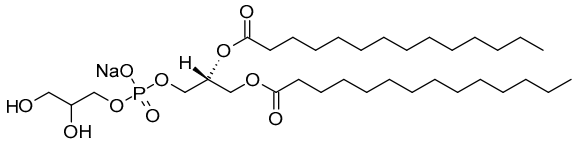
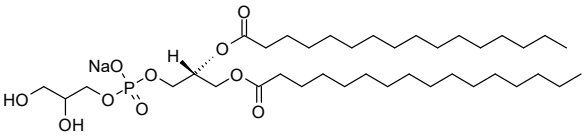
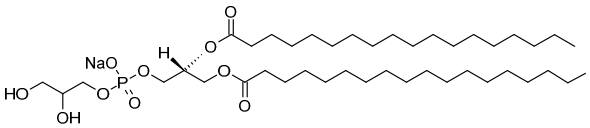
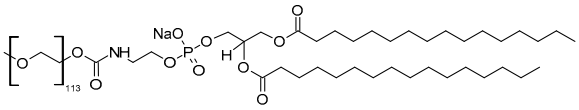
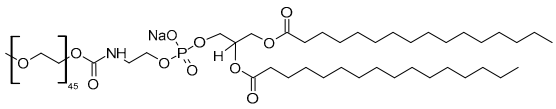
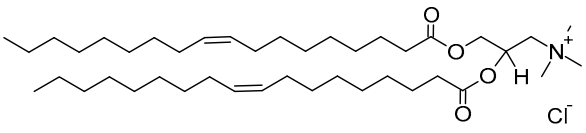
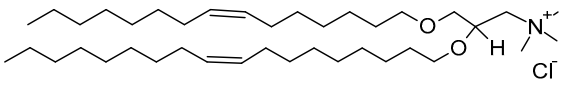
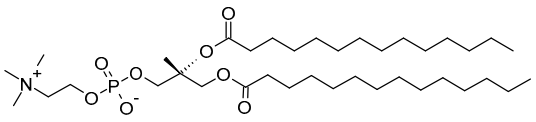
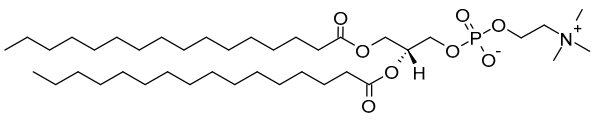
1,2-Dimyristoyl-*sn*-glycero-3-phosphoglycerol, sodium salt (CAS No.: 200880-40-6)	DMPG-Na	$C_{34}H_{66}NaO_{10}PNa$	
1,2-Dipalmitoyl-*sn*-glycero-3-phosphoglycerol, sodium salt (CAS No.: 200880-41-7)	DPPG-Na	$C_{38}H_{74}NaO_{10}PNa$	
1,2-Distearoyl-*sn*-glycero-3-phosphatidylglycerol, sodium salt (CAS No.: 200880-42-8)	DSPG-Na	$C_{42}H_{82}NaO_{10}PNa$	
N-(Methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylethanolamine, monosodium salt (CAS No.: 205494-72-0)	MPEG-5000-DPPE-Na	$(C_2H_4O)_nC_{39}H_{76}NO_{10}P$	
N-(Methoxypolyethylene glycol 2000 carbamoyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylethanolamine, monosodium salt (CAS No.: 384835-61-4)	MPEG-2000-DPPE-Na	$(C_2H_4O)_nC_{39}H_{76}NO_{10}P$	
Cationic			
1,2-dioleoyl-3-trimethylanmmonium-propane (chloride salt) (CAS No.: 132172-61-3)	DOTAP	$C_{42}H_{80}NO_4Cl$	
1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt) (CAS No.: 104872-42-6)	DOTMA	$C_{42}H_{84}ClNO_2$	
Zwitterion			
1,2-dimyristoyl-sn-glycero-3-phosphocholine (CAS No.: 18194-24-6)	DMPC	$C_{36}H_{72}NO_8P$	
1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine (CAS No.: 63-89-8)	DPPC	$C_{40}H_{80}NO_8P$	

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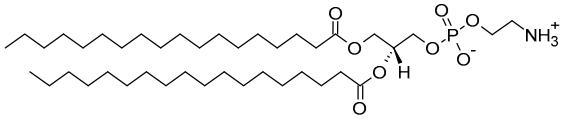
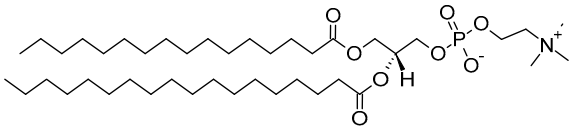
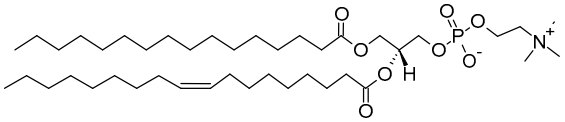
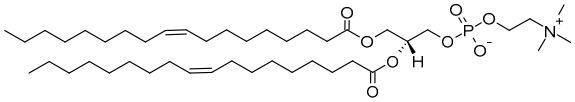
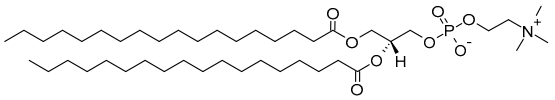
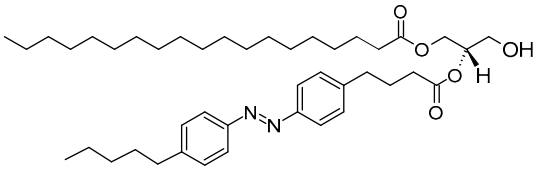
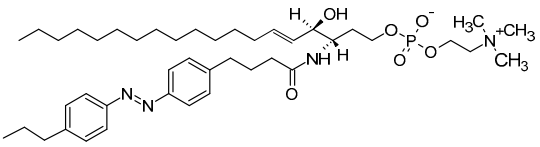
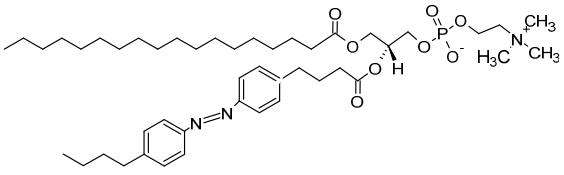
1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine (CAS No.: 1069-79-0)	DSPE	$C_{41}H_{82}NO_8P$	
L-*α*-phosphatidylcholine, hydrogenated (soy) (CAS No.: 97281-48-6)	HSPC	$C_{42}H_{84}NO_8P$	
1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (CAS No.: 26853-31-6)	POPC	$C_{42}H_{82}NO_8P$	
1,2-Dioleoyl-*sn*-Glycero-3-phosphocholine (CAS No.: 4235-95-4)	DOPC	$C_{44}H_{84}NO_8P$	
1,2-Distearoyl-*sn*-glycero-3-phosphocholine (CAS No.: 816-94-4)	DSPC	$C_{44}H_{88}NO_8P$	
Photoswitchable Lipids			
1-stearoyl-2-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-*sn*-glycerol (CAS No.: 1985595-31-0)	18:0-PhoDAG	$C_{41}H_{64}N_2O_5$	
N-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-D-erythro-sphingosylphosphorylcholine (CAS No.: 2260670-56-0)	Azo SM	$C_{43}H_{71}N_4O_6P$	
1-stearoyl-2-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-*sn*-glycero-3-phosphocholine (CAS No.: 2098674-45-2)	18:0-azo PC	$C_{46}H_{76}N_3O_8P$	

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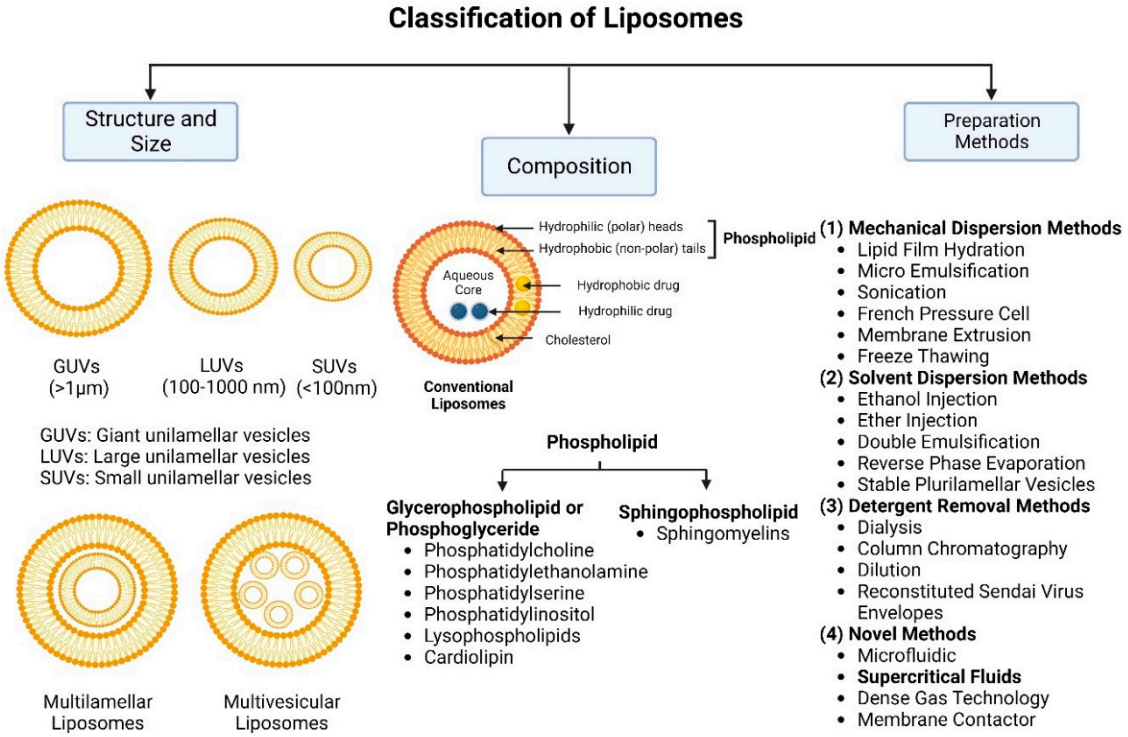

Figure 1. Classification of liposomes according to their structures, sizes, compositions, and preparation methods.

Phospholipids play key roles in the stability of liposomes in the systemic circulation, liposomal encapsulation and drug loading efficiency, as well as drug release at target sites. For instance, the use of 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) in the preparation of liposomes resulted in higher drug encapsulation efficiency compared to 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC). This was mainly due to the lengthy fatty acid chain of DSPC, as well as the rigidity of acyl chains of DSPC [10]. Furthermore, the use of *n*-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylethanolamine, monosodium salt (MPEG-5000-DPPE-Na) prolonged the blood circulation time of liposomes, owing to the additional steric hindrance of MPEG-5000-DPPE-Na, which reduced the liposomal uptake by the reticuloendothelial system (RES) [10]. Additionally, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoglycerol, sodium salt (DPPG-Na) exhibited fusogenic activity that improved the ability of liposomes to cross the cell membrane [11]. In general, liposomes can enter cells either by endocytosis (i.e., the process of capturing liposomes from outside by engulfing them with the cell membrane), or *via* exocytosis membrane fusion (i.e., the process where two phospholipid bilayers merge into a single continuous bilayer). Anionic liposomes showed faster endocytosis that enhanced their intracellular uptake, while fusogenic liposomes demonstrated an ability to fuse and penetrate the cell membrane [12]. Fusogenic liposomes are a particular type of liposomes, which are capable of causing fusion with biological membranes, thereby improving cell-type specific delivery and therapeutic efficacy. They are mainly composed of phospholipids, such as dioleoyl-phosphatidylethanolamine (DOPE) and cholesteryl hemisuccinate (CHEMS) [13]. On the other hand, the use of cholesterol in liposomes aims to provide additional rigidity to the bilayer system in order to enhance liposome stability throughout increasing the molecular packaging of phospholipid molecules, prompting drug retention inside the bilayer system and reducing the permeability of phospholipid bilayers [1,9]. In fact, cholesterol does not form bilayers by itself but will dissolve readily in the phospholipid-water bilayer system. The unique feature of liposomes is their ability to compartmentalize and encapsulate both hydrophilic and hydrophobic drugs. This unique feature

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along with biodegradability, biocompatibility, safety, non-toxicity and target-ability made liposomes very attractive nanocarriers to maximize drug delivery and activity [1,9].

There are several methods for the preparation of liposomes (Figure 1) [1,13], such as thin-film hydration (or thin-layer evaporation), reverse-phase evaporation, double emulsification, ether injection, ethanol injection, and detergent removal methods. However, all these techniques are used for the lab-scale production, and mostly require the use of organic solvents in high concentrations and ratios. Moreover, they exhibit difficulty in controlling size and intercalation efficiency. Supercritical carbon dioxide (SC-CO_2) (Figure 2) is a novel technique suitable for the large-scale production of liposomes with advantages of high encapsulation efficiency and uniform particle size distribution without the necessity of post-formation processes, such as sonication or extrusion [14]. In SC-CO_2, CO_2 is premixed with lipids, then entered a chamber with atomized water droplets. As a result of the high diffusion ability of CO_2 and the reduced viscosity of the solution, lipids would coat water droplets at higher rates, resulting in inverted micelle-like structures, which are further stabilized by another layer of lipids placed at the bottom of the chamber [14–16].

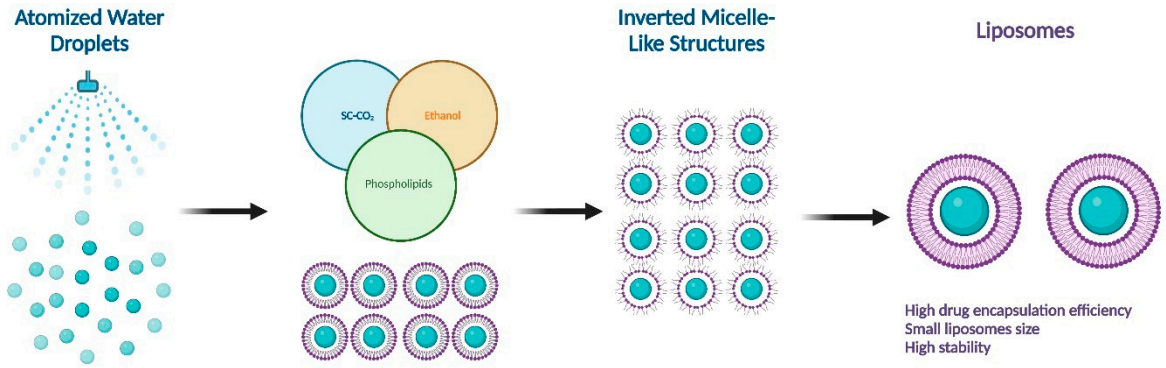

Figure 2. Supercritical CO_2 (SC-CO_2) assisted liposomes formation.

Numerous liposomal formulations have been clinically approved for human use to treat cancer and other chronic diseases, and are currently available in the global pharmaceutical market. Table 2 shows FDA and EMA-approved liposomal drug formulations [17,18]. The Orange Book identifies drug products approved on the basis of safety and effectiveness by the FDA [17]. The electronic medicines compendium (emc) identifies drug products approved for human use in the UK and Europe [18].

Table 2. FDA and EMA-approved liposomal drug formulations [17,18].

Product name	Approval date	Product description	Liposome composition	Indication and usage	Manufacturer
Doxil®	FDA: 1995 EMA: 1996	Doxorubicin encapsulated in stealth liposomes.	MPEG-DSPE, HSPC, cholesterol.	Ovarian cancer, AIDS-related Kaposi's sarcoma.	Janssen Pharmaceuticals
Abelcet®	FDA: 2005	Amphotericin B lipid complex injection.	DMPC, DMPG.	Invasive fungal infections.	Leadiant Biosciences, Inc.
DaunoXome®	FDA: 1996 EMA: 2004	Daunorubicin encapsulated in liposomes.	DSPC, cholesterol.	Advanced HIV-associated Kaposi's sarcoma.	Galen Ltd

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AmBisome®	FDA: 1997 EMA: 2006	Amphotericin B liposome for injection.	HSPC, cholesterol, DSPG, alpha tocopherol.	Cryptococcal meningitis in HIV infected patients.	Gilead Sciences, Inc.
DepoCyt®	FDA: 1999 EMA: 2001	Cytarabine liposome injection.	Cholesterol, triolein, DOPC, DPPG.	Lymphomatous meningitis.	Pacira Pharmaceuticals, Inc.
Myocet®	FDA: 2000 EMA: 2000	Non-PEGylated liposomal doxorubicin.	Phosphatidylcholine, cholesterol.	Metastatic breast cancer in adult women.	Teva Pharmaceuticals
Mepact®	FDA: 2001 EMA: 2009	A liposomal suspension of mifamurtide.	POPC, OOPS.	High-grade resectable non-metastatic osteosarcoma.	Takeda Pharmaceuticals
Exparel®	FDA: 2011 EMA: 2021	Bupivacaine liposome injectable suspension.	Cholesterol, DPPG, DEPC.	Postsurgical regional analgesia.	Pacira Pharmaceuticals, Inc.
Onivyde®	EMA: 2016	Irinotecan sucrosofate in PEGylated liposomes.	DSPC, cholesterol, MPEG-2000-DSPE.	Metastatic adenocarcinoma of the pancreas.	Laboratoires Servier (Servier)
Vyxeos®	FDA: 2017	Cytarabine and daunorubicin liposome injection.	DSPC, DSPG, cholesterol.	Acute myeloid leukemia.	Jazz Pharmaceuticals
Arikayce®	FDA: 2018 EMA: 2020	Amikacin liposome inhalation suspension.	Cholesterol, DPPC.	Non-tuberculous mycobacterial (NTM) lung infections.	Almac Group
Zolsketil®	EMA: 2022	Doxorubicin in PEGylated liposomes.	MPEG 2000-DSPE, HSPC, cholesterol.	Ovarian neoplasms, sarcoma, Kaposi, multiple myeloma.	Accord Healthcare S.L.U.

1.2. Targeting Mechanisms of Liposomes

The tumor-targeted delivery of liposomes can be achieved by two main targeting mechanisms: passive and active targeting.

1.2.1. Passive Targeting of Liposomes

In passive targeting mechanism, liposomes transport through the tumor interstitium to the target cells through capillary fenestrations and channels by passive diffusion or convection [19]. The tumour angiogenesis induces irregularities in endothelial cells with different pore sizes, ranging from 100 nm to 2 μm [13]. The differences in pore sizes and size distributions between the tumor

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microvasculature of endothelial cells and the tighter structures of normal cells make liposomes more easily accessible to the cancerous sites. Additionally, liposomes exploit the enhanced permeability and retention (EPR) effect for tumor targeting by improving the amounts of drugs delivered to tumor sites [20]. In order to passively target liposomes to tumor cells, liposomes should possess some physical and structural characteristics, such as (1) the size of liposomes should be in the range of 10-100 nm, (2) they should carry neutral or anionic charge in order to avoid the renal elimination, and (3) they should be protected from the RES [19–21].

1.2.2. Active Targeting of Liposome

Site-specific drug delivery is a method of targeting drugs to specific sites in a manner that increases their therapeutic indexes and reduces their possible side effects and toxicities [13]. Liposomes can reach tumor sites passively through the EPR effect [20], while the surface-modified (or surface-engineered) liposomes act by binding to specific receptors overexpressed by cancer cells, such as epidermal growth factor receptor (EGFR), folate receptor (FR), transferrin receptor (TFR), and other receptors (Figure 2) [19]. Since targeting the overexpressed surface receptors of cancer cells in order to enhance cellular uptake and intracellular activity is a promising approach, several cell surface strategies have been developed so far, aiming towards achieving targeted inhibition of these receptors [19,20]. The efficiency of active targeting and ligand receptor interaction are dependent on certain factors [22], such as (1) the extent of receptor expression level on tumor cells relative to non-tumor cells, (2) the availability of surface receptors on tumor cells, (3) the internalization rate, and (4) the heterogeneity of receptor expression in tumor cells. Active targeting can be achieved by surface engineering of liposomes *via* decoration with aptamers (oligonucleotides), carbohydrates, glycoproteins, monoclonal antibodies (mAbs) and their fragments, peptides, proteins, or other small molecules adsorbed onto the liposomal surface [19,21]. Figure 3 shows surface modification of liposomes for active targeting. Figure 4 shows the distinction between passive and active targeting. Table 3 shows some examples of liposomes and their ligands used for active targeting.

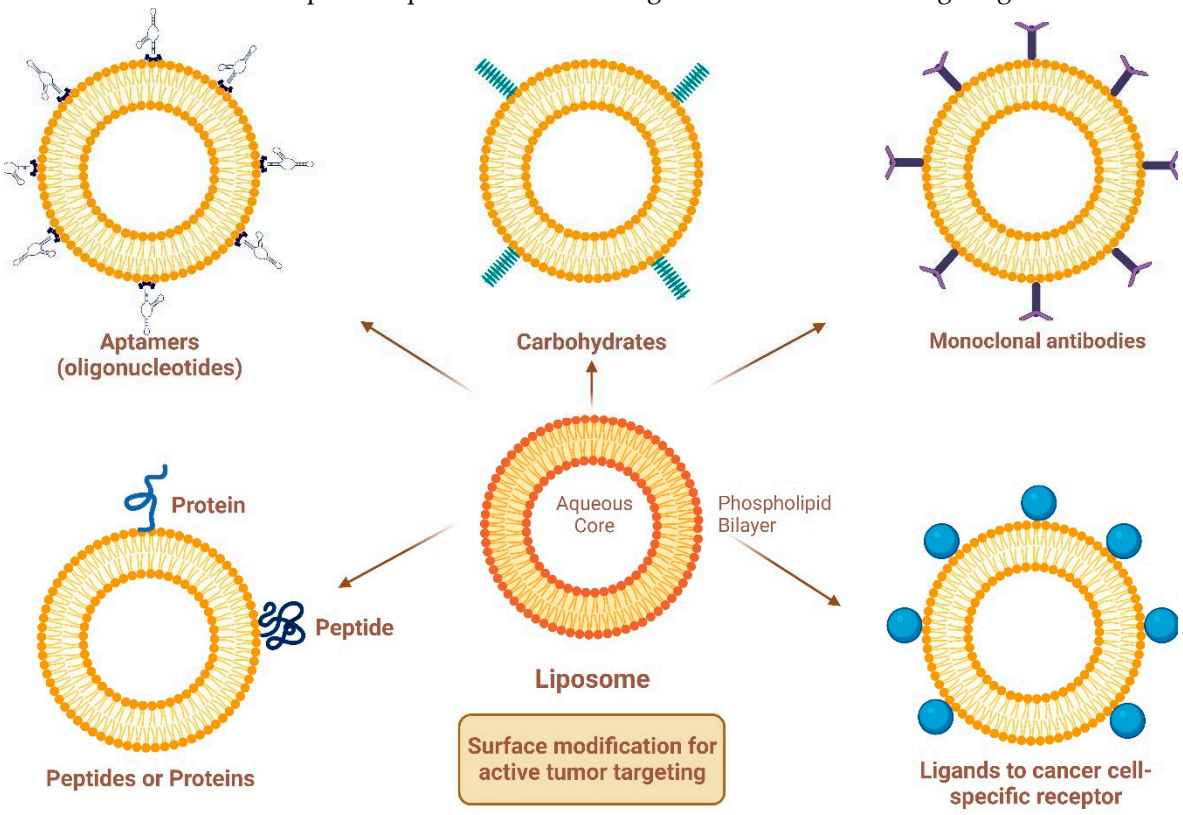

Figure 3. Surface modification of liposomes for active targeting.

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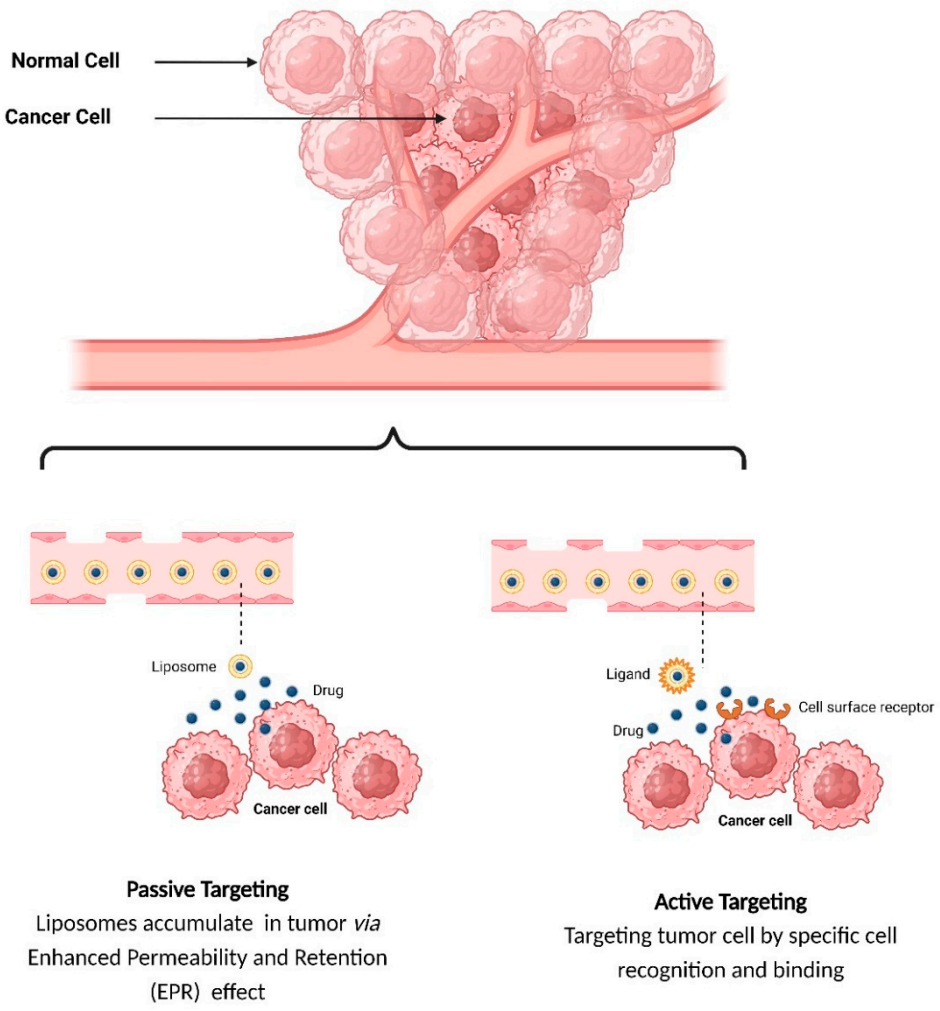

Figure 4. Targeting mechanisms of liposomes.

Table 3. Examples of liposomes and their ligands used for active targeting.

Active targeting ligand	Encapsulated drug	Preparation method	Reference
PEGylated Liposomes			
mAbs	Doxorubicin	Thin-film hydration	[23]
mAbs	Doxorubicin	Ethanol injection	[24]
Folate	Oleuropein	Thin-film hydration	[25]
Folate	Rapamycin	Thin-film hydration	[26]
Folate	Arsenic trioxide	Thin-film hydration	[27]
Transferrin	Plumbagin	Thin-film hydration	[28]
Transferrin	Resveratrol	Thin-film hydration	[29]
Mannose	Chlorogenic acid	Thin-film hydration	[30]
RGD	microRNA	Thin-film hydration	[31]
Cationic Liposomes			
Transferrin	Doxorubicin	Ethanol injection	[32]
mAbs	Curcumin	Thin-film hydration	[33]
Aptamer	Paclitaxel and siRNA	Thin-film hydration	[34]

mAbs: Monoclonal antibodies; **RGD:** Arginine-glycine-aspartic; **RNA:** Ribonucleic acid; **siRNA**: Small interfering RNA.

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1.3. Functionalized Liposomes

Functionalized liposomes include long-circulating PEGylated liposomes, targeting ligand functionalized liposomes, and stimuli responsive liposomes (Figure 5).

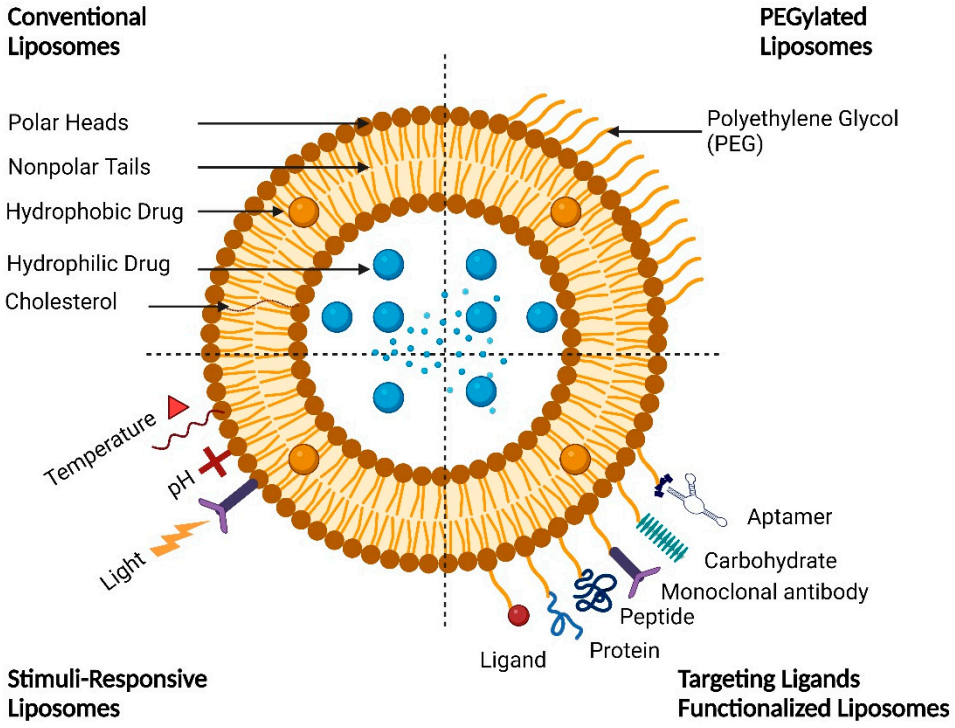

Figure 5. A schematic representation of conventional and functionalized liposomes.

1.3.1. Long-circulating PEGylated Liposomes

Effective targeting requires to design smart drug delivery systems with a long circulatory half-life (i.e., remain in the bloodstream for longer periods of time), which means that liposomes must evade uptake by RES organs. This unique character can be imparted onto liposomes by coating their surfaces with polymers that suppress opsonization by plasma proteins [35]. These liposomes are commonly known as stealth or long-circulating liposomes, owing to their stealth properties that make them resistant to recognition and degradation by enzymes and immune systems [35,36]. The most commonly used polymer to prevent liposome opsonization is polyethylene glycol (PEG). The process of PEG attachment to liposomes is called PEGylation [36]. Of note, PEG; commercially known as macrogol, is a hydrophilic, biodegradable polymer with a general formula of $H(OCH_2CH_2)_nOH$, where n is the number of oxyethylene groups + 1 [37]. There are different grades of PEG available in the global pharmaceutical market, such as PEG-400, PEG-1500, PEG-4000, PEG-6000 and PEG-20000 that differ in their molecular weights. PEGs with molecular weights of 1000 and higher are solid grades, and are ranging in their consistencies from pastes to waxy flakes, while PEGs with molecular weights below 1000 are viscous liquid grades [37]. The adsorption of PEGs onto the liposomal surfaces leads to enhance their blood circulation time, reduce their RES uptake, increase their biodistribution and target accumulation, and enhance the formulation stability [38]. However, despite all these advantages, PEG-functionalized liposomes showed some serious drawbacks. For instance, PEG demonstrates potential immunogenicity, owing to the activation of complement in response to antibodies [39,40]. In fact, PEG-based delivery systems support the phenomenon of accelerated blood clearance (ABC), owing to the formation of anti-PEG Immunoglobulin M (IgM) antibodies by the spleen after initial administration. Following the second administration, the anti-PEG IgM binds to PEG groups on the surface of liposomes, resulting in activation of the complement system, which subsequently leads to opsonization of the liposomes by C3 fragments, and consequently enhance the cellular uptake of liposomes by the Kupffer cells in liver, which in turn

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greatly affects the drug's bioavailability [39,40]. Even though the ABC phenomenon poses a significant challenge for certain drugs, it does not pose a critical problem for PEGylated liposomes used in cancer therapy, owing to the high lipid content of liposomes encapsulating anticancer cytotoxic agents [40].

1.3.2. Ligand Functionalized Liposomes

The adsorption of active targeting moieties on the surface of liposomes has played a significant role in enhancing liposomal accumulation in cancer cells, since this structural characteristic helps to increase the therapeutic index of the encapsulated drug, maximize on-target and minimize off-target effects. Briefly, active targeting is a surface modification process where active targeting moieties are adsorbed onto the liposomal surfaces, which substantially help to recognize and bind specifically to target cells through ligand-receptor interactions [41]. Actively targeted liposomes are made by grafting moieties, such as aptamers, carbohydrates, glycoproteins, mAbs and their fragments, peptides, proteins, and small molecules adsorbed onto the liposomal surfaces (Figure 3). The targeting moiety can be either inserted directly into the lipid membrane or attached specifically to the distal end of the polymer [35,42]. A recent trend in liposome surface functionalization includes the decoration of the liposomal surface with two ligands (i.e., dual-targeting). Dual-targeted liposomes offer numerous advantages, such as targeting multiple receptors, delivering more than one drug to target sites, enabling the encapsulated drugs to exert enhanced therapeutic effects, and reducing normal tissue toxicity and damage [43,44]. Dual targeted liposomes will be discussed in further detail later in this review.

1.3.3. Stimuli-ResponsiveLiposomes

Liposomes can respond to different internal and external stimulus, and thus can trigger the release of encapsulated drugs in a controlled manner to specifically target cancer cells. Internal stimuli include enzyme, pH, redox and temperature [45,46], while external stimuli include light, electrical-field, magnetic-field and ultrasound-waves [45,46]. Light, in the UV-visible-IR region, is a very promising tool for biological and medical applications due to its non-invasive nature, high spatial resolution and temporal control, tuneability over a wide range of wavelengths, convenience and ease of application, and robustness [47]. In comparison with other stimuli, light provides unparalleled spatiotemporal modulation of molecular processes [48], making it highly suitable for clinical and therapeutic applications [47,48]. Table 4 summarizes the advantages and limitations of different types of stimuli. Light-responsive liposomes have been recently introduced as smart, intelligent drug targeting delivery systems to target drugs for specific sites with high spatial and temporal control over drug release. These systems utilize nonionizing radiation and are mainly composed of biocompatible, biodegradable materials that can be straightforwardly tailored to the target sites for clinical and therapeutic applications [49]. Although most light-responsive liposomes respond to UV irradiation that has poor tissue penetration and high phototoxicity, optical technologies like laparoscopic tools are now commonly used for reaching deeper-located tissues. On the other hand, NIR is safer for use, causes less cell damage, and has good tissue penetration. However, the lower energy of NIR may be not efficient to induce the desired drug release response from liposomes [47,48].

Table 4. Comparison between different types of stimuli.

Stimuli	Advantages	Limitations	Reference
Light	- Sequentially trigger multiple payloads. - High degree of spatiotemporal precision. - Operate over a broad spectrum of wavelengths.	- Low penetration for UV- and visible light. - Overexposure to UV/visible irradiation can cause serious health problems.	[50,51]

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		- NIR penetrates tissues more deeply but with lower energy.	
Heat	- Suitable for cancer cells, which are highly sensitive to hyperthermia. - Enhanced tumor vascular permeability. - Reduced hypoxic conditions. - Intrinsically safe and effective.	- Risk of superficial tissue damage. - Difficult to spatially control hyperthermia at the tumor site.	[52,53]
pH	- Highly sensitive and specific. - pH-sensitive strategies allow site-specific drug delivery.	- Slow kinetics of drug release. - A small change in the pH can cause instability of the nanocarrier system.	[54,55]
Electrical-fields	- Iontophoresis devices generate safe levels of electrical fields with different strengths. - Readily accessible in the clinic.	- Risk of healthy tissue damage. - Electro-responsiveness is greatly affected by several environmental factors, such as composition of aqueous medium, types and concentrations of electrolytes.	[56,57]
Magnetic-fields	- Magnetic-controlled drug release with high precision. - Iron oxide materials are commonly used in magnetic-triggered drug delivery due to their biocompatibility.	- Complex installation and operating system. - Potential toxicity from metals. - Difficult to focus alternating magnetic field.	[58,59]
Ultrasound-waves	- Non-ionizing safe radiation with high penetration. - Minimal safety risks with low intensity, short exposure, and high degree of spatiotemporal precision.	- Ultrasound-responsive medium (gas/PFC) is required. - Risk of healthy tissue damage. - Drug-carrier instability issues.	[60,61]

In this review, the up-to-date targeting strategies and mechanisms of light-triggered drug release from liposomes and NIR-responsive nanocarriers are discussed in light of surface functionalization and target structures. Moreover, we highlight recent key advances in design and application of light-responsive liposomes and dual-targeted stimuli-responsive liposomes. Lastly, we outline the current challenges and future perspectives for the deployment of light-responsive liposomes in targeted drug delivery and therapy. Our overall aim is to provide a step towards developing next generations of light-responsive liposomes and dual-targeted stimuli-responsive liposomes.

2. Mechanisms of Light-Triggered Drug Release from Liposomes

Light-triggered mechanisms that can be exploited to release encapsulated drugs from liposomes are photoisomerization, photocleavage (photo-oxidation), surface plasmon resonance absorption

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(photothermal activation), photochemical hydrophobicity change (photochemical activation), and photo-crosslinking and de-crosslinking (Figure 6).

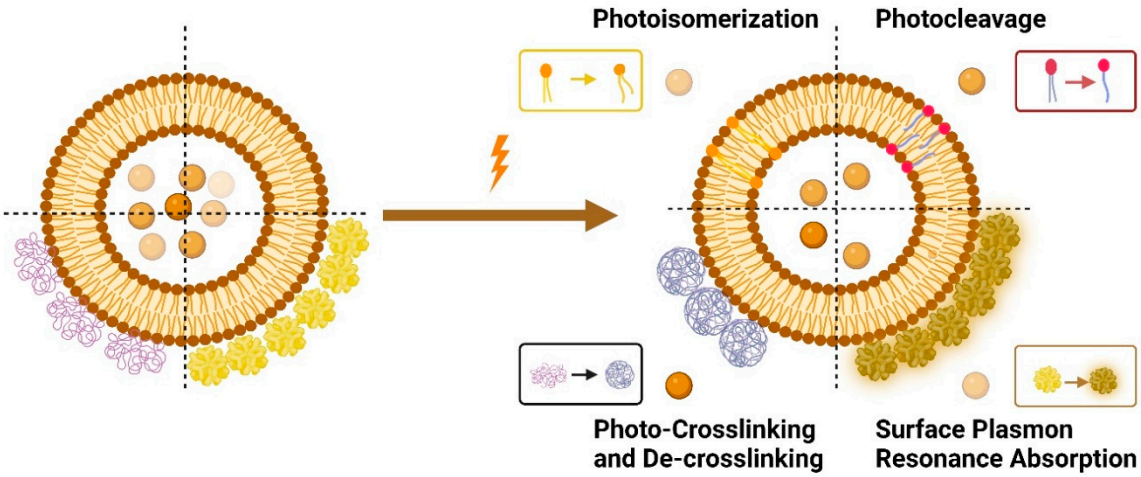

Figure 6. Light-triggered mechanisms used in triggering drug release from liposomes.

2.1. Photoisomerization

Photoisomerization is a photo-induced isomerization process from one isomeric form to another (i.e., *cis (Z)*- to *trans (E)*-isomer). It is worth mentioning that *trans (E)*-isomers are more stable and lower in energy than *cis (Z)*-isomers due to no electrical repulsion, since the two larger groups are far as possible from each other; while in the case of *cis (Z)*-isomers, the two larger groups bump into one another, resulting in an electrical repulsion [62]. When photo-responsive molecules are irradiated with UV-light, they undergo conformational changes from *trans*- to *cis*-isomers. These conformational changes make the structural integrity of liposomes more permeable, owing to the steric hindrance, as well as the increased polarity of *cis*-isomers [62]. The transition from *trans*- to *cis*-isomer can be triggered by UV-light irradiation at wavelengths ranging from 320-350 nm, and the reverse transition can be triggered by visible light irradiation (400-450 nm) or by heat.

Azobenzene, spiropyran and diarylethene are the most commonly used photoswitches in photoisomerization-based drug release [63,64]. Azobenzene undergoes a UV-light induced double-bond isomerization to its metastable *Z*-isomer, which is characterized by being shorter in length, bent, twisted and more hydrophilic than *E*-isomer. Spiropyran (carrying a neutral charge) undergoes a UV-light induced ring-opening reaction to its zwitterionic metastable form, which is commonly known as merocyanine, and is characterized by being more hydrophilic. While diarylethene undergoes a UV-light (6π) electrocyclization and ring-closing reaction to its thermally stable isomer, which is characterized by being conjugated and rigid in structure; however, the ring-closed isomer can be reopened again, using visible light (Figure 7) [63,64].

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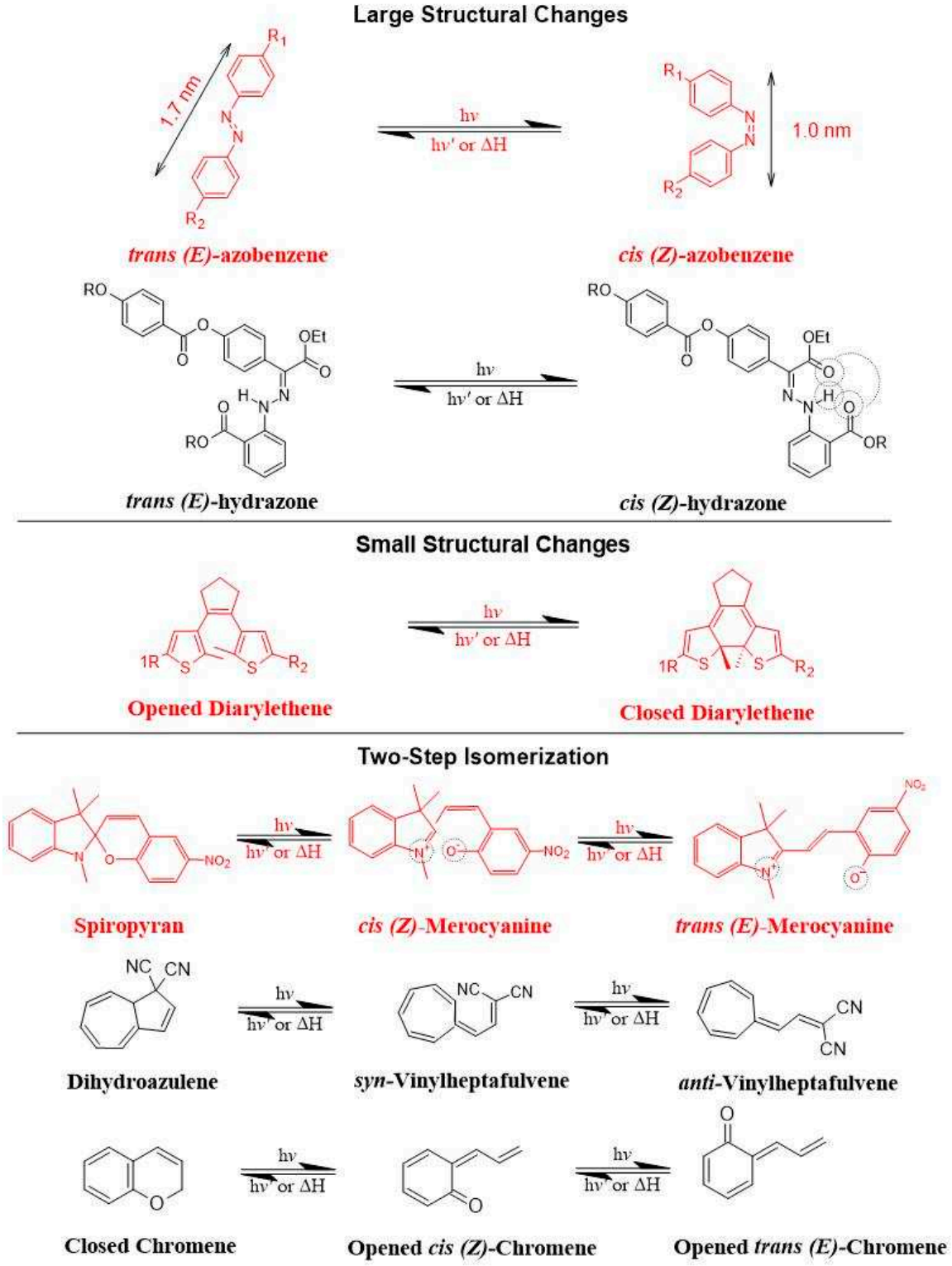

Figure 7. The most common photoswitches and their photoisomerization reactions.

There are preferred application areas for each photoswitch. For example, azobenzenes are superior photoswitches when large structural and geometrical changes are required [65]. Complementary to azobenzenes, diarylethenes show small structural and geometrical changes but large electronic changes upon photochemical interconversion between the ring-opened and closed structures [66]. Spiropyrans offer unique properties in respect to ring-opening and closing isomerization, owing to their molecular dipole moments which increase during photoconversion processes from the ring-closed to opened structures (Figure 7) [67].

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The mechanism of *trans-cis* photoisomerization has been used to induce drug release from light-responsive liposomes. As an interesting example of photo-response mechanism of azobenzene photoswitch in liposomes, Li *et al.* [68] developed a novel liposomal curcumin formulation with photoswitching properties, owing to the presence of 4-butylazobenzene-4-hexyloxy-trimethyl-ammoniumtrifluoro-acetate (BHA) as a photo-responsive reversible switch. The azo-group of BHA was capable of undergoing a reversible *trans-cis* isomerization under UV and visible light irradiation. BHA-curcumin-liposomes, abbreviated BHA-cur-lipo, were prepared by the thin-film hydration method along with SC-CO_2 technique. The percent encapsulation efficiency (EE%) of curcumin in BHA-cur-lip was ~88%. Curcumin was released from BHA-cur-lipo under UV-light irradiation; ~90% curcumin was released within 6 hours. BHA embedded in the liposomal bilayer was able to isomerize under UV-light irradiation, and the isomerization process was capable of repeating multiple times. The isomerization of BHA in the liposomal bilayer could be used as a switch to precisely controlled on-demand drug release.

As an interesting example of photo-response mechanism of spiropyran photoswitch in liposomes, Zhang *et al.* [69] developed photo-responsive liposomes composed of spiropyran-containing triazole-phosphatidylcholine (SPTPC). SPTPC was synthesized through a copper-catalyzed azide alkyne cyclo (CuAAC)-addition reaction. In an aqueous solution, SPTPCs self-assembled into vesicles due to the presence of phosphatidylcholine (PC), then spontaneous isomerization of spiropyran-to-merocyanine (SP-to-MC) occurred, resulting in co-occurrence of liposomes and fibers. The switching from spiropyran (SP) to merocyanine (MC) isomeric form induced a reversible transition between these molecular structures. Additionally, the authors studied the self-assembly properties of SPTPCs and photoinduced liposome–fiber assembly-transition and concluded that (1) the presence of MC allowed for additional intermembrane interaction during self-assembly, (2) the driving force for the assembly-transition was the MC-stacking effect. Exposure to UV-light at 365 nm induced switching from SP to MC isomeric form, where the planar structure and confinement of MC leads to enhanced MC-stacking. The MC-stacking effect had some advantages and drawbacks, such as MC-stacking disturbed the hydrophobic phase in the lipid bilayer and permitted the liposome-to-fiber transition, otherwise the MC-stacking blocked switching of MC to SP and caused an incomplete isomerization recovery from MC to SP during fiber-to-liposome recovery. Therefore, a fatigue of SP was observed during the liposome-to-fiber transition cycle. To suppress MC-stacking effect and minimize the intermolecular interaction, a photo-inert triazole-phosphatidylcholine (TPC) was subsequently added to make TPC/SPTPC-liposomes, which showed better recovery kinetics. The active photoadaptation behavior of TPC/SPTPC-liposomes confirmed the disturbance of the lipid bilayer by the formation of MCTPC-enriched phases in the lipid bilayer. Overall, the reversible liposome-to-fiber assembly-transition of SPTPC was a promising and potential candidate for adaptive assembly systems.

As an interesting example of photo-response mechanism of diarylethene photoswitch in liposomes, Liu *et al.* [70] synthesized a novel amphiphilic photoswitchable fluorescent probe of liposomes, namely, PEGylated perylenemonoimide-dithienylethene, abbreviated PEG-PMI-DTE, that exhibited excellent photochromic reversibility, fluorescence switching and fatigue resistance under UV and visible light irradiation. The fine nanostructures of liposomes (MLVs, LUVs and SUVs) were able to be observed directly under super-resolution optical microscope by the use of amphiphilic photoswitchable fluorophore as a staining agent, with an optical resolution of 30 nm. This research offers a new type of optical probe and optical approach to investigate nanostructures using photoswitchable fluorescent probes in super-resolution imaging.

2.2. Photocleavage (Photo-Oxidation)

Photocleavage is a photo-induced bond cleavage through photosensitized oxidation that can be achieved when the photosensitizer and oxygen are proximate to the oxidizable lipid in liposomes, which are characterized by having a lipid segment sensitive to singlet oxygen ($^1O_2$) produced by the photosensitizer [71]. The photocleavage release mechanism from liposomes occurs by lipid photo-oxidation that leads to membrane destabilization, disruption, and subsequently drug release [72].

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Briefly, when liposomes are irritated with light, photosensitizer will absorb photos, leading to be excited to the triplet state. This generates reactive oxygen species (ROS) that can be either in the form of radicals (hydroxyl ($HO^{\bullet}$) and superoxide ($O_2^{\bullet}$)) or non-radicals ($^1O_2$). Singlet oxygen ($^1O_2$) is a highly reactive oxidant with low stability and short half-life. It can oxidize different cellular constituents, such as nucleic acids, lipids and proteins [71,73]. Its tendency to induce toxicity can be precisely controlled.

The mechanism of photocleavage was explored through photodynamic therapy (PDT). PDT is a light-based cancer therapy that uses light to activate photosensitizers, leading to the generation of ROS or $^1O_2$. that are highly reactive oxidants which can mediate damage to tumor cells or tissues. The effectiveness of PDT depends on several factors [74,75], such as (1) the type of photosensitizer, (2) the intensity of light, (3) the route of administration, (3) tumor type, size and location, and (4) the concentration of dissolved cytoplasmic oxygen. The ideal photosensitizer should be [76,77]: (1) safe, effective and non-toxic, (2) water-soluble compound, (3) pharmacologically inactive in the absence of light source, (4) highly specific and selective, (5) have an absorption spectrum preferably between 650 nm to 800 nm, and (6) rapidly metabolized to inactive metabolite and discharged from the human body. Photosensitizers are categorized into two main classes: porphyrin photosensitizers and non-porphyrin photosensitizers [77]. Three generations of porphyrin photosensitizers exist. First-generation porphyrin photosensitizer includes hemaporphyrins, which have several drawbacks that limit their therapeutic use, such as: (1) chemical instability issues, (2) poor tissue penetration, (3) activation with light below 650 nm, (4) skin hypersensitivity reactions, (5) long half-life, and (6) low elimination rates [77]. Second-generation porphyrin photosensitizers include metalloporphyrins, porphycenes, purpurins, chlorins and protoporphyrins [77]. Second-generation porphyrin photosensitizers have been approved by the FDA and EMA for the treatment of cancer. For example, 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL, Metvix®, Galderma) are precursors of protoporphyrin IX, which absorbs at 630 nm. They are approved by the FDA for the treatment of prostate, bladder and colon cancers [17]. Meta-tetrahydroxy phenyl cholorin (m-THPC, Temoporfin, Foscan®, Biolitec Pharma) absorbs at ~652 nm, and is approved by the EMA for the treatment of biliary and pancreatic cancers [18]. Verteporfin (Visudyne®, Novartis), a benzo-porphyrin derivative, absorbs at 690 nm, and is approved by the FDA for the treatment of gastric cancer [17]. Coupling of the 2nd generation porphyrin photosensitizers with biologically targeting molecules, such as carbohydrates, peptides or antibodies resulted the 3rd generation porphyrin photosensitizers, which displayed high selectivity and specificity with minimal adverse effects [77]. Non-porphyrin photosensitizers include psoralens, anthracyclines, chalcogenopyrylium dyes, cyanines and phenothiazinium dyes [77]. Although all of the above advantages of PDT photosensitizers in the treatment of cancer, they are still suffering from serious drawbacks and limitations, such as poor biodistribution and cellular uptake of hydrophobic photosensitizers, difficulty in applying PDT to deeper tumor tissues, and low sensitivity and selectivity towards some cancer cells [74,75]. Therefore, PDT is only effective and suitable for treating superficial skin tumors.

Since the use of photosensitizers often cause serious skin hypersensitivity reactions, thus encapsulation of photosensitizers into nanocarrier systems, such as liposomes will overcome these problems. Of note, Sun *et al.* [78] developed anticancer liposomal chemophototherapy (CPT) using bilayer-loaded photosensitizer and anti-cancer drug cabazitaxel (CTX). Cabazitaxel-loaded porphyrin-phospholipid liposomes, abbreviated CTX-PoP-Lip, were prepared by the hot ethanol injection method in order to encapsulate the hydrophobic CTX within the lipid bilayers. Cholesterol and PEG-lipid were added to enhance liposomal stability and permeation. The EE% of CTX in CTX-PoP-Lip was ~60% and the percentage of loading capacity (LC%) was ~2%. Morphologically, CTX-PoP-Lip showed spherical, unilamellar vesicles with a diameter size of ~100 nm. CTX-PoP-Lip showed an optical absorption peak similar to PoP-Lip without CTX, with a characteristic PoP peak apparent at 420 nm (for the PoP Soret band) and 675 nm (for PoP Q-band). Upon excitation at 675 nm, a fluorescence peak was observed for both CTX-PoP-Lip and PoP-Lip. Without PoP, CTX-Lip had no fluorescence. Over 3-months of storage under 4 ^{o}C, CTX-PoP-Lip displayed good colloidal stability in terms of particle size, polydispersity and zeta potential. Moreover, CTX showed good

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photochemical stability under laser irradiation. Remarkably, the combination of CTX-PoP-Lip with laser treatment showed positive tumor inhibition therapeutic effect in comparison with PDT alone or chemotherapy alone.

Lipid-porphyrin conjugates are novel promising carriers for drug delivery with multifunctional properties. As a promising example of this conjugation system, Massiot *et al.* [79] designed phototriggerable liposomes-based on lipid-porphyrin conjugate and cholesterol combination. First, they synthesized a new lipid-porphyrin conjugate, termed PhLSM, by coupling pheophorbide-a (Pheo-a), a photosensitizer derived from chlorophyll-a, with egg lyso-sphingomyelin. The pure PhLSMs were able to self-assemble into vesicle-like aggregates, but they were highly unstable due to the mismatch between the length of the alkyl chain in *sn*-1 position and the adjacent porphyrin. Stable PhLSMs lipid bilayers were obtained by mixing PhLSMs with cholesterol. Based on these observations, the authors prepared stable liposomes encapsulated a hydrophilic fluorescence probe in the aqueous core. The prepared liposomes showed light-triggered cargo release in an ON/OFF fashion, which was attributed to their photothermal conversion. In addition to the light-triggered cargo release property and phototoxic photothermal effect, the prepared liposomes showed markedly high photothermal conversion efficiency and photostability.

2.3. Surface Plasmon Resonance Absorption (Photothermal Activation)

Photothermal approaches involve the conversion of light into heat to induce liposomal membrane permeabilization. Some metals exhibit unique optical properties, such as dielectric function, reflectivity and electron energy loss function, when present in the form of nanostructures as nanoparticles, or entrapped inside the nanocarrier systems as nanoparticles-loaded liposomes [80]. Metallic nanostructures are highly attractive multifunctional nanoplatforms, owing to their unique size- and shape-dependent properties. One of the most interesting characteristics of metallic nanostructures is their optical properties that are strongly dependent on particle size and shape [80]. For example, bulk gold metals look yellowish in reflected light, but thin gold films look blue in transmission. This characteristic blue colour gradually changes to orange through several tones of purple and red as a result of reducing particle size to ~3 nm. These changes are likely to account for the surface plasmon resonance (SPR) [80], which is defined as the frequency/wavelength at which conduction electrons oscillate in regard to the alternating external electric field (Figure 8). The optical properties of metallic nanostructures are controlled by the collective oscillation of conduction electrons, resulting from the interaction with the electric field of the incident light, owing to the presence of free conduction electrons [80,81]. The electric field of the incoming radiation creates a strong dipole electric field inside the metallic nanostructures. A restoring force in the metallic nanostructures attempts to compensate for this difference, resulting in a unique resonant wavelength.

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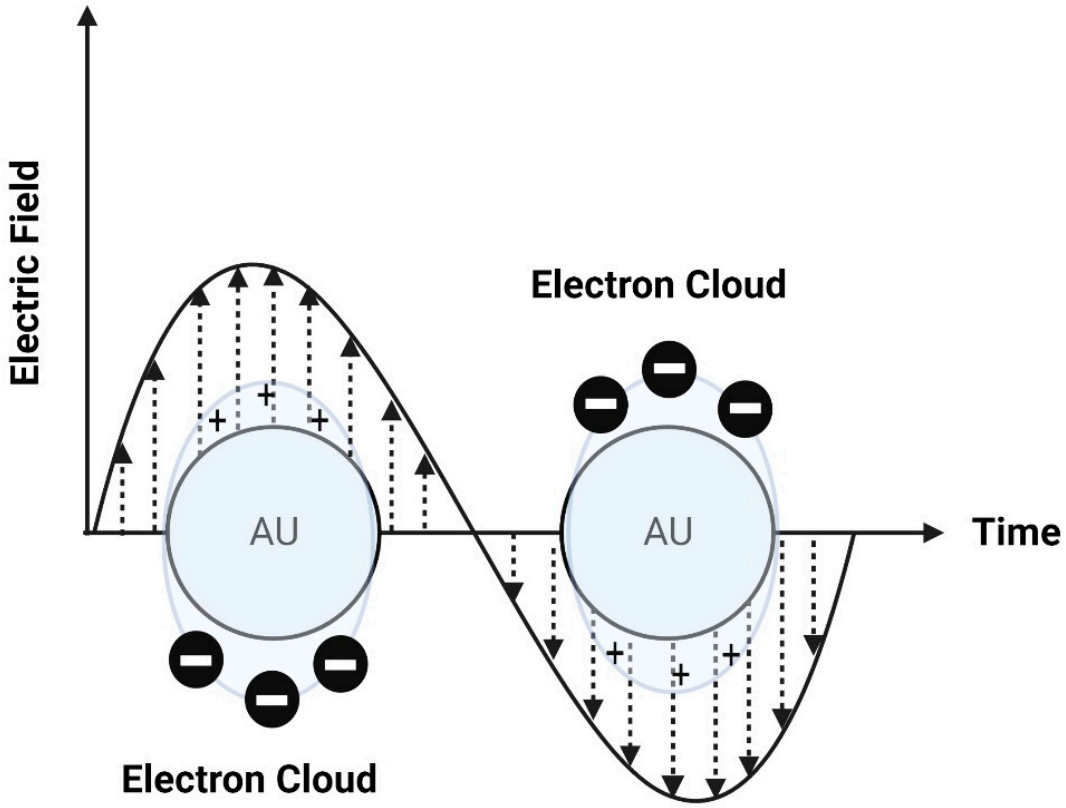

Figure 8. A schematic diagram of surface plasmon resonance (SPR).

The SPR frequency and intensity of metallic nanostructures are dependent on the electron charge density that is primarily affected by several factors, such as size, shape, structure, composition and the dielectric constant of surrounding environment.

Interestingly, Rubio-Camacho *et al.* [82] synthesized stable gold nanoparticles on the surface of DPPC thermosensitive liposomes, termed AuNPs@DPPC, resulting in the formation of nanohybrids with on-demand plasmon mode in the visible/NIR region and with good photothermal conversion efficiency. The AuNPs@DPPC nanohybrids retained the physical properties of DPPC thermosensitive liposomes without altering either the liposome fluidity or the hydration degree of the lipid bilayer. AuNPs@DPPC nanohybrids showed good light-to-heat conversion properties upon irradiation in the NIR region. These nanohybrids represented highly attractive and promising candidates in light-mediated therapies, such as NIR-light-controlled drug delivery. As an interesting example of gold nanoparticles-drug conjugates in liposomes, Li *et al.* [83] synthesized vincristine sulfate-conjugated gold nanoparticles incorporated into liposomes as a promising light-responsive hybrid nanocarrier system with enhanced antitumor efficiency. Gold nanoparticles were synthesized by reducing tetrachloroaurate, using trisodium citrate as the reducing agent. The amount of trisodium citrate used in the synthesis of gold nanoparticles was 1% to prepare uniform size-controlled nanoparticles. The resulting gold nanoparticles had a particle size of 17 nm. The conjugation of gold nanoparticles with vincristine sulfate was achieved *via* ionic bonding, since vincristine sulfate is positively charged, while the citrate-capped gold nanoparticles were negatively charged. The highest EE% was achieved when vincristine: gold nanoparticles molar ratio was 6:100. The conjugates were incorporated into liposomes by film dispersion to yield nanoparticles of 113.4 nm with UV-light-responsive controlled release properties. Interestingly, UV irradiation had also considerably increased intracellular drug release, cytotoxicity, and apoptosis in HeLa cells. *In-vivo* studies in tumor bearing nude mice showed that the therapeutic efficacy of vincristine was enhanced after exposure to UV-light, with relatively high tumor inhibition rate and low toxicity. The accumulation of the drug selectively at the tumor

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site (by EPR effect of liposomes), together with light-responsive controlled release represented an important step forward in tumor targeting drug delivery.

2.4. Photochemical Hydrophobicity Change (Photochemical Activation)

Amphiphilic block copolymers have a relatively high potential to produce nanostructures (either micelles or vesicles) *via* self-assembly in suitable solvent systems [81]. Polymeric micelles are thermodynamically stable when the concentration of polymers is above the critical micelle concertation (CMC) value. If the concentration of polymers is below the CMC value, micelles will disintegrate, dissolve and release their payloads. Thus, in such case, polymeric micelles are thermodynamically instable [81]. Therefore, various techniques were developed and applied to improve the thermodynamically stability of polymeric micelles. Foremost among these techniques is a photochemical activation method-based on changing the hydrophobicity of molecules [81]. Briefly, this mechanism depends on increasing the CMC value and dissolving the micelles by converting the amphiphilic polymers to more hydrophilic forms, thus providing a controlled drug release [81]. Interestingly, light-responsive chromophores, such as azobenzene, spiropyran, diarylethene and their derivatives can be incorporated inside the micellar cavity, where NIR can be used to induce chemical transformation to a more hydrophilic form [83]. Most of light-responsive chromophores can absorb UV-light; however, NIR is more suitable for biomedical applications, owing to its capability to penetrate deeply into tissues (up to 10 cm), with a low potential for tissue damage [83]. Self-assembled polymeric micelles are used as amphiphilic particulate emulsifiers for controllable Pickering emulsions. Pickering emulsions have been aroused unprecedently in drug delivery. However, engineering tunable Pickering emulsions with the capability of responding to light still remains very challenging. Interestingly, Zhao *et al.* [84] designed a photo-controllable nanocarrier system to control the amphiphilicity of Pickering emulsifiers, using a β-cyclodextrin-grafted alginate polymer and an azobenzene derivative. Briefly, a biocompatible alginate polymer grafted with β-CD (*via* Ugi reaction), abbreviated Ugi-Alg-CD, was first synthesized and used as an amphiphilic macromolecule surfactant host. Then, azobenzene coupled with polyethylene glycol (Azo-PEG) was prepared and used as a guest molecule. By coupling Ugi-Alg-CD with Azo-PEG, a stable Pickering emulsion was successfully fabricated. The photoisomerization of a host-guest complex between β-cyclodextrin and azobenzene derivative was customized to regulate the polarity of the microenvironment. Interestingly, the photoactivatable emulsifier-based on supramolecular self-assemblies was able to undergo destabilization of O/W emulsions by changing the amphiphilic balance of host-guest assemblies at the O/W interface under UV-light irradiation, resulting in phase separation. Analysis of the microstructures of self-assemblies at the O/W interface during the demulsification process indicated that the reversible light-triggered *trans-cis* isomerization of Azo-PEG likely resulted in the regulation of the hydrophilic-hydrophobic balance of supra-amphiphilic polymer emulsifiers. This photochemical strategy opened the door to develop novel photo-responsive nanocarrier systems for various biomedical applications. However, to the best of our knowledge, this mechanism has not been reported in liposomes.

Polymersomes are biomimetic cell membrane-like bilayer vesicles that are self-assembled stepwise from amphiphilic block copolymers. They are analogous to liposomes, but with outstanding properties, such as higher chemical stability towards oxidation and hydrolysis reactions and greater resistant to mechanical deformation processes within the human body like bending and stretching (i.e., resistance to high shear rates of blood circulation and deformations during blood flow through microvessels) or cellular processes (e.g., division and fusion) [86]. Besides, other properties, such as composition, size, shape and surface chemistry that resulted in increased EE% and LC% (i.e., polymersomes have lower membrane fluidity and higher viscosity due to the presence of amphiphilic block copolymers which contribute to the low permeability of encapsulated drugs from the inner core of polymersomes to the outer site [86,87]. Polymersomes can disassemble in response to light for controlling the release of encapsulated drugs that may also respond to light. Thus, polymersomes can provide spatiotemporal control of drug release. Interestingly, Yamamoto *et al.* [88] studied the structure-function relationships and photo release characteristics of different types of photo-

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responsive polymersomes composed of amphiphilic di-block copolymers. The building blocks of these photo-responsive polymersomes were hydrophobic polymers and poly(ethylene glycol) with photocleavable 2-nitrobenzyl compounds bearing alkyne and maleimide moieties. Interestingly, all polymersomes preserved their hollow structures even after light irradiation. Additionally, polymersomes with a 2-nitrosobenzyl photolysis residue within the hydrophobic shells showed photo-induced drug release after complete photolysis. The authors concluded that the drug release was controlled by photo-induced permeability changes of the hydrophobic shells rather than the decomposition of their molecular structures.

2.5. Photo-Crosslinking and De-Crosslinking

The mechanism of photo-crosslinking-induced drug release occurs through the polymerization of unsaturated bonds located in the hydrophobic domain of the lipid bilayer. When photo-responsive polymerizable moieties are irradiated with light at a specific wavelength, the crosslinking reaction between them causes the shrinkage of the lipid bilayer in the surrounding domain where the photosensitizers are present. This causes bilayer disruption by altering lipid packing; as a result, conformational changes occur, leading to increased membrane permeability and drug release rates [84]. The mechanism of photo-crosslinking was first reported in liposomes by Regen *et al.* [89]. Liposomes were prepared with a photo-triggerable lipid containing two methacrylated phosphatidylcholine derivatives. The resulting liposomes were more stable than non-crosslinked type, and displayed prolonged blood circulation and enhanced tumor accumulation and retention. More interestingly, Nakamura, *et al.* [90] described the transportation of deoxyribonucleic acid (DNA) into liposomes using ultrafast photo-crosslinking. The cohesion of the DNA adsorbed onto the liposomal surface induced transformations in the liposomal structure and allowed phototriggered, sequence-specific DNA transportation into liposomes. This technique was a useful tool for specific delivery of nucleic acid drugs.

The reversible photo-decrosslinking is a promising emerging alternative to optimize target-specific drug binding. Photo-decrosslinking was first reported in 2009 by He *et al*. [91], who formulated a nanogel made with a di-block copolymer (PEO-*b*-P(MEOMA-co-CMA) composed of polyethylene oxide (PEO) and a coumarin-containing poly(2-(2- methoxyethoxy)ethyl methacrylate) (P(MEOMA-co-CMA). Crosslinking was achieved by using UV-light at 310 nm, while de-crosslinking was achieved by irradiating at wavelength 260 nm. Recently, Lu *et al.* [92] developed a photo-responsive microgel that can be reversibly photo-crosslinked and de-crosslinked using UV-light of 2 different wavelengths. This microgel was prepared by precipitation copolymerisation of 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA), methacrylic acid (MAA) and 7-(2-methacryloyloxyethoxy)-4-methylcoumarin (CMA). The effective crosslinker CMA can be photo-crosslinked by irradiation with UV-light at 365 nm and photo-decrosslinked by irradiation with UV-light at 254 nm. To understand the photoswitching mechanism, the volume-phase transition temperature (VPTT) was monitored during transitions. The authors concluded that there was a significant change in VPTT that led to a uniform distribution of CMA within the microgel interior. The photo-induced swelling behavior of the microgel was employed to control the release of anticancer drug doxorubicin. This research study opened the door to develop new hybrid systems of liposome-in-gel as promising carriers for cancer therapy.

3. Mechanisms of NIR Light-Triggered Drug Release

Light-triggered drug release from liposomes is mainly dependent on the penetration depth of the selected light source, the photophysical properties of the incorporated photo-responsive molecule, as well as the chemical composition and surface properties of the liposomal nanocarrier [93]. Several radiations have been used to trigger drug release, such as UV, visible and NIR. However, the preferred wavelengths for therapeutic and biomedical applications are found in the NIR region (~700 to 1100 nm); since at these wavelengths, the light penetration depths are more than 1 cm [94]. The main mechanisms of drug release from NIR-responsive liposomes are photothermal effect, two-photon absorption (TPA), and up converting nanoparticles (UCNPs) (Figure 9).

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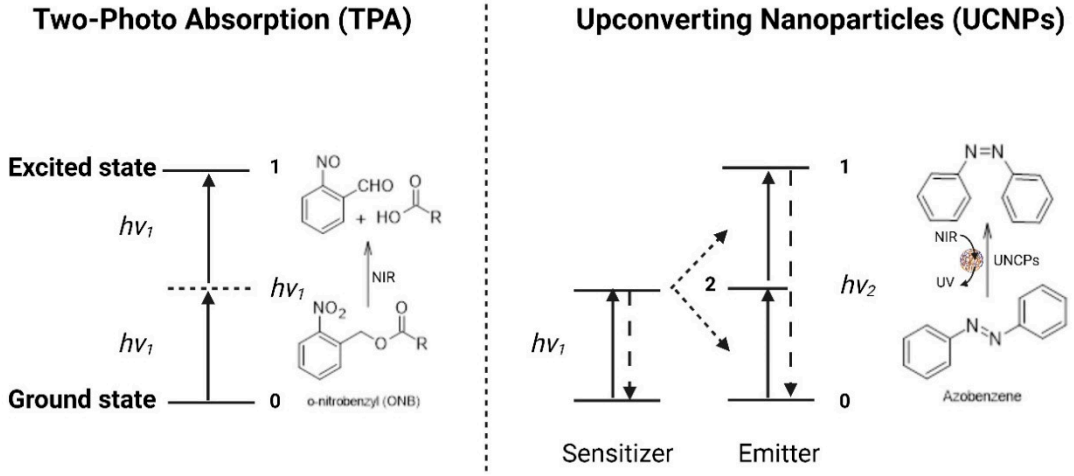

Figure 9. A schematic representation of the energy transfers processes of two-photon absorption and NIR-mediated up conversion.

3.1. Photothermal Effect

The photothermal effect encompasses the conversion of light to heat by a photothermal agent loaded inside the liposomal nanocarrier. This heat stimulates the heat-responsive material inside the liposomal nanocarrier and disrupts the liposomal structure, either by disturbing the hydrophilic-lipophilic balance (HLB), or by creating a phase transition that leads to drug release at the target site. For example, Li *et al* [95]. prepared nanostructured lipid carriers (NLCs) encapsulated in liposomes containing the hydrophilic CXCR4 antagonist plerixafor (AMD3100) and the hydrophobic NIR-photothermal agent IR780. The NIR-light stimulated IR780 to produce heat that caused disruption of the lipid bilayer, resulting in complete nanocarrier disassembly and subsequent drug release. In addition, IR780 induced cytotoxic hyperthermia as a synergistic effect along with chemotherapy. More interestingly, Refaat *et al.* [96] developed a NIR-activated thermosensitive liposomes encapsulated ultrasmall gold nanorods and non-ionic surfactant (Brij® 58) for protein delivery. The prepared nanohybrid carrier system showed significant increase in thermosensitivity due to the thermosensitive property of gold nanorods, which resulted in the rapid release of encapsulated proteins. Consequently, this system was selected for encapsulation, on-demand release and delivery of the thrombolytic agent, urokinase-plasminogen activator (uPA). Urokinase light-responsive liposomes exhibited enhanced thrombolytic effect (80.7% lysis of an *in-vitro* halo-clot model in 30 min following NIR irradiation (785 nm, 1.35 W/cm^2 for 5 min)) compared to free uPA and non-irradiated liposomes (36.3% and 15.5%, respectively). Overall, the newly engineered, gold nanorod-based NIR light-responsive liposomes represented a promising drug delivery system for on-demand, site-directed, and photothermally-stimulated therapeutic protein release.

3.2. Two-Photon Absorption (TPA)

Two-photon absorption (TPA) relies on the excitation mechanism induced by two absorbed photons [97]. Briefly, the chromophore is excited from its ground-state to excited-state *via* simultaneously absorbing two photons with equal energy, then it undergoes a specific photochemical reaction [98,99]. In the case of chromophores with a wide NIR absorption spectrum, such as 2-diazo-1,2-naphthoquinone (DNQ), coumarin, and o-nitrobenzyl (ONB), they can be initiated by NIR-light to undergo specific photoreactions, such as rearrangement and photocleavage reactions *via* TPA process. Then, the chromophore-functionalized nanocarriers will be destroyed as a result of the changes in molecular structures, leading to drug release (Figure 9). For example, Sun *et al.* [100] developed NIR-responsive liposomes composed of cholesterol, the NIR-responsive lipid made by incorporating the NIR-light-responsive 6-bromo-7-hydroxy-4-hydroxycoumarin (Bhc) unit into the lipid acyl chain, and POPC. The prepared liposomes were able to encapsulate the hydrophilic

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molecules in the liposome interior cavity, and release their cargos upon NIR irradiation. Drug release from liposomes were controlled by adjusting the percentage of photo-responsive lipid or through irradiation parameters (time and intensity), demonstrating a potential controlled drug release action. This study provides evidence for developing efficient photo-responsive drug and gene delivery systems.

Although TPA is a promising technique for controlled drug delivery, owing to the high spatial and temporal resolution, deep tissue penetration, and low scattering of NIR-light, this technique requires a focal pulsed laser with high energy density in order to treat a small infection area. Thus, this method is not suitable for *in-vivo* experiments.

3.3. Upconverting Nanoparticles (UCNPs)

The upconverting nanoparticles (UCNPs) process encompasses the conversion of NIR- to UV-light [101]. Briefly, the UCNPs is a process of multi-photon excitation that involves at least two excitation photons, where the absorption of these photons is sequential and not simultaneous. The low-energy NIR can be converted into high-energy UV-light by the UCNPs, which would isomerize the azobenzene chromophore from *trans-* to *cis*-isomer (Figure 9) [102]. For more efficient energy transfer, the emission band of UCNPs should overlap the absorption band of the chromophore as much as possible [103]. For example, Xiang *et al.* [104] prepared UCNPs with an amphiphilic di-block copolymer containing a UV-sensitive inner hydrophobic layer composed of poly(4,5-dimethoxy-2-nitrobenzyl methacrylate) and an outer hydrophilic layer composed of poly(methoxy polyethylene glycol monomethacrylate). When UCNPs irradiated with NIR-light at 908 nm, the amphiphilic di-block copolymer absorbed the UV-light and induced a disturbance of the HLB, leading to rapid nanocarrier disassembly and drug release [104]. Once the poly (4,5-dimethoxy-2-nitrobenzyl methacrylate) (PNB) absorbed UV-light, the hydrophobic block polymer converted into hydrophilic block polymer, leading to the dissolution of the di-block copolymer and releasing of the drug molecules. Some NIR-responsive carrier systems use a photosensitizer to create a synergistic effect by producing ROS in addition to chemotherapy [105,106].

4. Strategies for Light-Targeting Drug Delivery

Regarding strategies for light-targeting drug delivery, three main strategies are generally employed, which are light-targeting through activation of targeting ligands, light-targeting through particle size reduction, and light-targeting through blood vessel disruption.

4.1. Light-Targeting through Activation of Targeting Ligands

Light-targeting through activation of targeting ligands enables the active targeting of liposomes through the activation of targeting ligands present on the surface of liposomes, leading to cellular binding following light irradiation. In order to develop a liposomal nanocarrier with light-triggered active targeting, it should (1) temporarily deactivate targeting ligands circulating in the blood stream, and (2) expose the targeting ligands following light irradiation at a specific target site [107]. There are two basic routes by which the targeting ligands can be temporarily deactivated: (1) caged ligands, by using photocleavage groups to chemically cage the ligands, and (2) shielded ligands, by using molecular chains to physically shield the ligands [107]. Light irradiation can then activate the ligands by the removal of caging or shielding groups (Figure 10). Table 5 shows some examples of light-targeting though activation of targeting.

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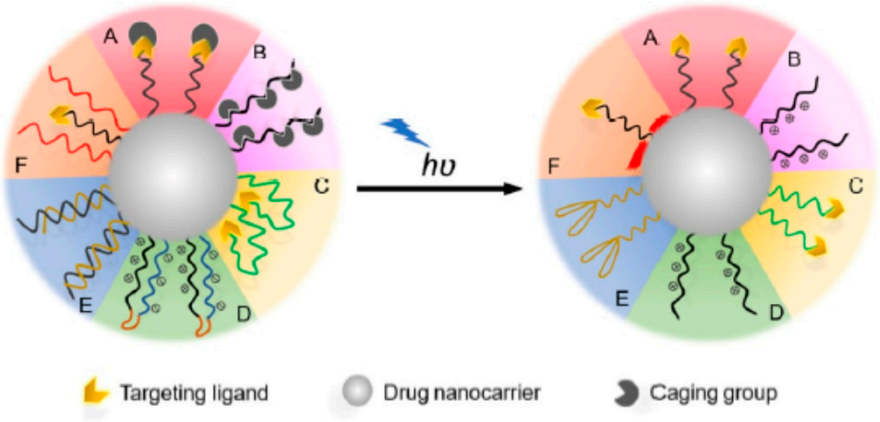

Figure 10. A schematic representation of light-targeting mechanism through activation of targeting ligands. **A:** Caging of the ligand binding sites; **B:** Caging of the ligand electrical charge; **C:** Anchoring of the ligands inside the nanocarrier system; **D:** Neutralizing the ligand charge by electrostatic interactions; **E:** Shielding of aptamer ligands through the use of complementary oligonucleotides; **F:** Shielding of the ligands using thermo-responsive polymers. In all aforementioned cases, the ligand is either caged or shielded in the nanocarrier system. Upon light irradiation, it is exposed onto the surface of the nanocarrier system to allow for active targeting. Figure adapted with permission from [107].

Table 5. Examples of light-targeting though activation of targeting ligands of liposomes.

Encapsulating Drug	Ligand type	Caging/Shielding group	Irradiation source	Reference
siRNA	CPP/PCP	PEG	NIR	[108]
Vinorelbine bitartrate	PSP/NGR	PEG	NIR	[109]
-----	TAT	PEG	UV	[110]
siRNA	pcCPP/NGR	PEG	NIR	[111]
5(6)- carboxyfluorescein	AMP (BTL)	ε-amino group of the Lys in TL	UV	[112]
Paclitaxel	Folate	o-nitrobenzylamine	UV	[113]

siRNA: Small interfering RNA; **CPP:** Cell penetrating peptide (CGRRMKWKK); **PCP: P**hotolabile-caged peptide (CGRRMK^{PG}WK^{PG}K^{PG}); **PSP:** Photosensitive peptide (CGRRMK^{PG}WK^{PG}K^{PG}); **NGR:** Asparagine–glycine–arginine (CYGGRGNG); **TAT:** Transactivating transcriptional activator (YGRKKRRQRRRG); **PEG:** Polyethylene glycol; **pcCPP:** Photolabile-caged cell-penetrating peptide; **AMP:** Antimicrobial peptide, **BTL:** Bhcmoc-temporin L; **Bhcmoc:** 6-bromo-7-hydroxycoumarin-4- ylmethyloxycarbonyl.

4.2. Light-Targeting through Particle Size Reduction

Nanocarrier size can influence the tumor accumulation and penetration capacity in the tumor microenvironment. In general, nanocarriers with an average size below 100 nm are preferred to achieve deep tissue penetration, site-specific release and targeted drug delivery [114]. Light can be used to reduce the particle size of nanocarriers, thereby enhance tissue penetration and increase tumor-targeting efficiency. For instance, Tong *et al*. [115] designed light-responsive nanohybrids made of PEGylated lipid and alkyl chain-conjugated spiropyran that were capable of shrinking upon UV irradiation, and thereby achieved deep tissue penetration. Upon UV irradiation at 365 nm, the hydrophobic spiroyran transformed from the neutral spiroyran to zwitterionic merocyanine, resulting in the nanohybrids inner cores' structural rearrangement (Figure 11). The particle size reduction promoted the release of the encapsulated drug at its target site.

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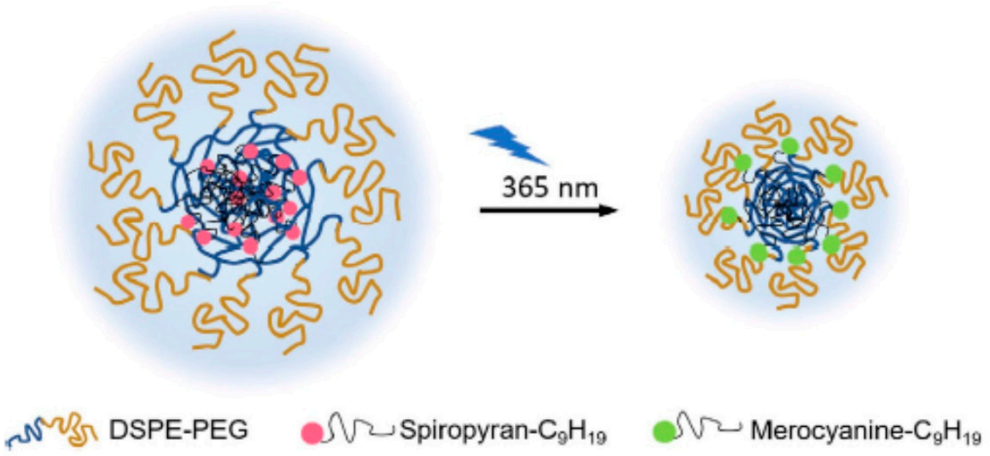

Figure 11. Light-targeting through particle size reduction strategy. The neutral spiropyran changes to the zwitterionic merocyanine following UV irradiation, resulting in nanoparticle rearrangement and size reduction. Figure adapted with permission from [107].

Interestingly, light-targeting through particle size reduction strategy can also be used for effective targeting of intracellular organelles, e.g., Golgi vesicles, lysosomes and nuclei [107]. However, in order to target the nucleus, the nanocarrier system should be able to penetrate the cell nucleus *via* nuclear pores which have pore sizes of 9-40 nm. Since nanocarriers with average sizes of less than 10 nm are quickly removed from the blood stream by renal filtration [116], Qiu *et al.* [117] developed a light-responsive gold nanoparticles containing doxorubicin as anticancer drug and cell type-specific internalizing aptamers to effectively target the cell nucleus. Upon NIR irradiation at 808 nm, the self-assembled structures of nanoparticles were disassembled due to the photothermal effect of NIR-light, leading to the release of the drug from the nanocarrier system.

4.3. Light-Targeting through Blood Vessel Disruption

Light-targeting through blood vessel disruption improves EPR-mediated drug targeting to tumors [118]. This strategy comprises three main approaches: photodynamic therapy (PDT), photothermal therapy (PTT), and photoimmunotherapy (PIT). As mentioned earlier, PDT involves the use of dyes that are excited to a higher energy singlet state from which they do intersystem crossing to a triplet state that is suitable for energy transfer to molecular oxygen ($^3O_2$), forming singlet oxygen ($^1O_2$) or other reactive oxygen species (ROS) [119,120]. PDT can damage tumor endothelial cells, increase vascular permeability, and thereby improve the EPR effect and drug delivery to the tumor site [10,119,120]. In turn, PTT utilizes light to generate heat from plasmonic nanoparticles to kill the tumor cell (Figure 12). While in the case of PIT, it utilizes antibody-photosensitizer conjugates that precisely bind to cells in the immediate perivascular space [121]. PIT can damage tumor cells through photosensitization, increase vascular permeability, and thereby improve drug delivery at the tumor site. For example, Sano *et al.* [122] developed panitumumab-photosensitizer conjugates. Upon IR irradiation at 690 nm, a high leakage rate of nanoconjugates (10 – 200 nm) into A431 (human epidermoid carcinoma) cell line was resulted, indicating the potential of PIT to enhance nanodrug delivery in tumors.

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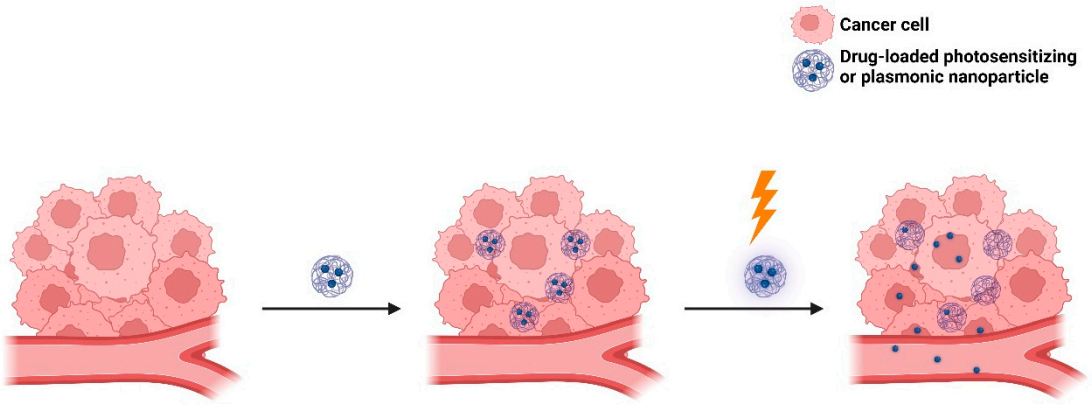

Figure 12. A schematic representation of the enhanced intra-tumoral accumulation of nanocarriers using PDT or PTT.

5. Light-Responsive Liposomes for Drug Delivery

Light-responsive liposomes have been introduced as a smart nanocarrier for spatiotemporal control of drug release. Hence the triggering feature of light-responsive liposomes greatly enhanced the therapeutic efficacy and minimized possible side effects of therapeutics. Light-triggered drug release from liposomes can occur through two main approaches: (1) photo-destabilization/disassembly of the liposomal structure, and (2) light absorption of metallic nanoparticles. In the case of photo-destabilization/disassembly of the liposomal structure, different photosensitisers can cause membrane destabilization and permeabilization. They can be strategically incorporated into lipid bilayers. Modification of phospholipids can occur in potential sites, e.g., the hydrophilic polar heads, glycerol backbone and fatty acyl side chains [123,124]. The drug release can be through one of the previously mentioned mechanisms of light-triggered drug release from liposomes (Figure 6). While in the case of incorporating metallic nanoparticles into liposomal structure, these nanoparticles can be localized within the lipid bilayers, on the surface of liposomes, aggregate in the core of liposomes, or be free in the aqueous or buffer compartment [125,126]. Upon irradiation of liposomes, nanoparticles convert the absorbed photon-energy to thermal-energy, leading to the instability of the liposomal structure [125,126].

5.1. Formulation Design and Optimization

To design optimal liposomes for drug delivery, it is important to consider certain factors within the liposomal structure, such as size, lamellarity, surface charge, bilayer fluidity and liposomal surface modification. To endow liposomes with photoactivation properties, additional photophysical properties should be considered, such as the type and concentration of photoswitch embedded in lipid bilayer membranes, the photosensitizer hydrophobicity and membrane localization (i.e., photosensitizer-membrane interactions), the spectral and photosensitizing properties of the photosensitizer used, the wavelength of the selected light source and its penetration depth. Most of these parameters were discussed earlier in this review, while other parameters will be discussed below in detail.

5.1.1. Liposomal Size

The liposome size considers one of the most important parameters in the design of optimal liposomes, since liposome biodistribution, tumor accumulation and clearance are primarily dependent on the liposome size. Moreover, the liposome size affects the immunogenicity and plasma half-life of the liposomal drug nanocarrier, thus affecting the drug circulation time and tumor targeting. In addition, the size of liposomes influences their endocytosis, thereby affecting the intracellular distribution and drug activity [127]. The excretion of liposomes is mainly through liver

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and kidney, where kidney elimination is faster than liver elimination. Liposomes with small particle sizes (<5 nm) are mainly eliminated through the kidney, while liposomes with large particle sizes (up to 100 nm) are mainly eliminated through the liver due to the fact that larger particle sizes can be easily engulfed by macrophages [128,129]. In fact, liposomes with small particle sizes are not easily cleared by the phagocytes of mononuclear phagocyte systems (MPS), but they can be rapidly eliminated by the kidney. Overall, liposomes with particle sizes between 5 and 100 nm have longer circulation time [128,130].

5.1.2. Surface Charge

The surface charge of liposomes is primarily dependent on the head group of the liposomal phospholipid, and it can be either negative, neutral or positive. Negatively charged phospholipids or anionic liposomes are easily recognized by macrophages, and they can enter cells *via* endocytosis at a higher rate than neutral phospholipids, resulting in a shorter circulation time. On the other hand, positively charged phospholipids or cationic liposomes are rapidly cleared from the blood circulation through complement activation or opsonization. Thus, anionic liposomes are preferred for preclinical studies and are common to most FDA and EMA-approved liposomal formulations. Overall, the zeta potential of liposomes (< –30 mV, or >30 mV) is considered physically stable due to electrostatic repulsive forces [131].

5.2. Light Source Selection

The light sources commonly used in photo-responsive nanocarriers are UV (200– 400 nm), visible (400–700 nm), and NIR (700–1000 nm) lights. UV-light is the most widely used light source because it can provide sufficient energy to trigger most of photochemical reactions (e.g., isomerization, cleavage crosslinking or de-crosslinking reactions) [50]. Nevertheless, the use of UV-light is accompanied by some serious disadvantages related to tissue penetration depth and phototoxicity. Therefore, the potential use of UV light-responsive nanocarriers in clinical applications are very limited. In contrary, NIR-light has deeper tissue penetration depth due to the minimal attenuation and refraction by endogenous chromophores and biomolecules [49,51]. Although NIR-light possesses advantages of deeper tissue penetration and lesser damage to normal cells, only few compounds are able to respond to NIR-light directly, owing to the low energy of NIR-light which is insufficient to trigger photochemical reactions [49,51]. To solve this problem, the nanocarriers that can convert incident NIR-light to UV-light have been developed. The resulting UV-light can allow photochemical reactions, resulting in effective drug release. The conversions of lower energy NIR photons to higher energy UV photons encompass the processes of TPA [97–99] and UCNPs [101–103].

5.2.1. Light Penetration Depth

The selection of the proper wavelength of the light source determines the tissue penetration depth. Therefore, it is important to select a suitable light source with an optimal wavelength to induce tumor-specific photoactivation. In general, the penetration depth increases along with wavelengths, which can range from a few hundred microns of UV-lights to (>5 mm) of NIR-lights [132]. UV-lights are preferred for the treatment of early-stage (superficial) cutaneous cancers, while NIR-lights for late-stage (deep) cutaneous cancers [133].

5.2.2. Photodamage

The excessive use of UV-light causes photolesions that distort the DNA double helix structure and thus leads to DNA damage, which eventually results in cancers. [134]. In turn, the long exposure to visible light induces cell receptor and retinal photodamage [135]. On the other hand, NIR-light possesses the advantages of deeper penetration depth in tissues, as well no or less DNA damage and genotoxicity [136]. Therefore, most of current research on light-responsive liposomes is focused on using NIR-light.

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6. Dual-Targeting Stimuli-Triggered Liposomes

Over the last few decades, researchers have attempted to make the liposomal nanocarriers more tumor specific and effective by combining two or more stimulus in a single drug-loaded vehicle, leading to the development of dual-targeted liposomes. Dual-targeted liposomes have several advantages over conventional liposomes, such as target two or more receptors, better tumor cellular internalization, release the encapsulated drugs at higher efficiency and accuracy, and avoid normal tissue toxicity [137]. By combining two different stimuli in one liposomal formulation, site-specific and multistage targeting can be precisely achieved.

6.1. Light/pH Dual-Responsive Liposomes

As a selected example of combining light with pH stimuli, Kong *et al.* [138] developed a biodegradable multifunctional nanoplatform of photothermal-responsive calcium carbonate particles coated with pH-responsive acetalated dextran and phospholipid, abbreviated AuNR@CaCO3@POPC-AcDX as a novel nanoplatform for the incorporation of both hydrophilic and hydrophobic molecular targeted therapeutics, with high EE% and LC%. The AuNR@CaCO3@POPC-AcDX hybrid nanoplatform was effective in the growth inhibition of cancer cells with specific molecular targeting, and overcome multidrug-resistance and possible adverse drug reactions. The photothermal effect promoted the therapeutics ultrafast release and speedy cancer cells death. Another interesting selected example, Chen *et al.* [139] designed a pH-sensitive charge-conversional and NIR-responsive bubble-generating liposomal complex, named bubble-generating thermosensitive liposomes (BTSL) made of cypate, doxorubicin and poly(methacryloyl sulfadimethoxine) for synergetic thermo-chemotherapy for tumors. The cationic liposomes containing cypate, doxorubicin and NH_4HCO_3 were first shielded by pH-sensitive poly(methacryloyl sulfadimethoxine) through electrostatic interaction at physiological pH 7.4. Then, at pH 6.5 (reflecting the tumor microenvironment), PSD was de-shielded; as a result, the liposomal formulation displayed pH-sensitive charge reversal capability. The doxorubicin was released from PSD/DOX/Cypate-BTSL by NIR irradiation. After NIR irradiation, the hyperthermia induced by cypate was capable of producing CO_2 bubbles owing to the decomposition of NH_4HCO_3, resulting in a robust drug release. In 4T1 breast cancer cells, PSD/DOX/Cypate-BTSL improved cellular uptake and cytotoxicity.

6.2. Light/Temperature Dual-Responsive Liposomes

As a selected example of combining light with temperature, You *et al.* [140] developed a novel liposomal formulation containing cisplatin, indocyanine green (ICG) and CJM126 mixed with cholesterol derivative (CJM-Chol) for the purpose of synergistic chemo-photothermal therapy. Liposomes were prepared by the thin-film hydration method. The prepared liposomes showed a uniform diameter of 103.8 nm and good polydispersity of 0.195. Irradiation with NIR induced photothermal conversion, which triggered rapid drug release from liposomes. Outstandingly, the light-induced heat-initiated drug release at temperature >42 °C accelerated the drug release and made it more controllable. Moreover, the prepared liposomes showed significantly excellent inhibitory effect (3.05% cell viability in 24 hours) on MDA-MB-231 breast cancer cells when irradiated with NIR-light as compared with free cisplatin (28.41%) or treatment without NIR (11.24%), which was significantly superior to chemotherapy or photothermal therapy alone. Another interesting selected example, Lu *et al.* [141] prepared gold nanoshells-coated oleanolic acid liposomes (GNOLs) mediated by chitosan. The GNOLs were spherical in shape with a uniform diameter size of 72.03 nm and zeta potential of 20.7 mV, which were more likely to be accumulated at the tumor site. The GNOLs exhibited a slow release of oleanolic acid at pH 7.4, while robust release at pH 5.5, which was favourable for tumor-triggered drug release. Under NIR irradiation, hyperthermia was produced by activated gold nanoshells, which triggered drug release from liposomes by modulating the gel to liquid crystalline phase transition of liposomes. On the advantage of the photothermal effect of gold nanoshells and thermal-sensitivity of lipid bilayers of liposomes, the lipid coat was destabilized after NIR irradiation, and a robust drug release was achieved. Because of the pH-responsive of the cationic

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polymer chitosan, the encapsulated drug was able to identify drug targets easily, and achieve intracellular tumour site-specific drug release. The novel gold nanoshells coated oleanolic acid liposomes mediating tumor therapy represented a potentially important advancement in chemo-photothermal therapy.

7. Challenges in Light-Triggered Drug Release from Liposomes

Despite all advantages of light-responsive liposomes, there are still challenges associated with UV- and NIR-light that limit their use and application. For instance, the use of UV-light is often associated with a high risk of tissue damage that is not limited to tumor tissues, but also to surrounding normal tissues, and thereby may eventually lead to therapeutic failure and incomplete tumor eradication [51,52]. Though NIR is more preferable in drug delivery and release; however, the low energy wavelength light of NIR may be not sufficient to induce photochemical effects [51,52]. Other emerging challenges in light-based therapy include increasing the tissue penetration depth of incident light, increasing tumor selectivity of the used photosensitizer, improving the efficacy and efficiency of photo-responsiveness and optimizing the switch-on and switch-off transitions [142].

On the other hand, although remarkable progress has been made during the last few decades in the design and development of nanocarrier systems, there are still some challenges in their clinical research. For example, the size of most nanocarriers ranges from 10 – 100 nm, owing to some technical limitations related to their preparation methods [143]. It is worth mentioning that nanocarriers with sizes ≥ 200 nm are primarily accumulated in extracellular spaces, while nanocarriers with sizes ≤ 10 nm can easily be filtered out [143]. The major challenges in clinical research of nanocarriers lie in finding the right target for disease diagnosis, the proper drug for disease treatment and the most suitable targeting strategy for site-specific drug delivery [144]. In the matter of light-responsive liposomes, the methodological complexity of light-responsive liposomes hinders their industrial scale-up, thus new industry-oriented methods are necessary for the synthesis and application of smart generation light-responsive liposomes. Moreover, the lack of clinical data related to safety and efficacy of light-responsive liposomes *in-vivo* greatly limits their widespread therapeutic use; therefore, more clinical trial data are necessary to further advance the clinical significance of light-responsive liposomes.

8. Emerging Trends and Future Prospects

Clinical applications of light-responsive liposomes are limited by light penetration depth; however, new advancements in light technology, such as fiber optic endoscopy (FOE), enabled the temporary placement of optics to target deep tissues [95]. Moreover, novel strategies in photo-responsiveness, such as the development of photocleavable groups that are capable of either being activated by long-wavelength lights or by efficient up-conversion systems, or that contain photo-protecting groups with red-shifted absorption led to improve tissue penetration depth [145–147]. With regards to photosensitizers, the modification of photosensitizer core by substitutes led to wavelength-shifting to the blue-green region [148]. Moreover, the high efficiency triplet–triplet annihilation (TTA) up-conversion systems were fabricated to tolerate with large stocks shifts [149]. For example, Huang *et al.* [149] designed a TTA up-conversion system of long-wavelength light from the far-red (600 – 670 nm) to the deep-blue (410 – 500 nm) region for efficient activation of photo-responsive molecules. On the other hand, the combination of light with other triggers was able to increase the triggering precision [150]. For instance, Lin *et al.* [151] developed a light-activated hypoxia-responsive drug delivery system in which the encapsulated drug was bonded to 7-aminocoumarin through a photocleavage bond. Additionally, nitroimidazole, an electron acceptor was coupled to 7-aminocoumarin in order to prevent bond breakage upon irritation, owing to photo-induced electron transfer (PET) phenomena. The nitro-to-amino hypoxia-specific reduction converted nitroimidazole to aminoimidazole, leading to losing PET effect. Once at the tumor site and under hypoxic conditions, the drug was released from coumarin conjugate following light

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irradiation. This design increased tumor-targeting selectivity and reduced the toxicity to healthy tissues surrounding the tumor.

9. Conclusions

Tuning the release and activity of drug nanocarriers *via* the application of light represents an innovative technology and approach in the field of drug delivery, since it allows for optimum spacing, precise bonding timing and accurate positioning between drugs and their receptors, and therefore, delineates the optimal configuration of the nanocarrier system with enhanced physicochemical and photophysical characteristics. Photo-responsive nanocarriers have recently received increasing attention as smart drug nanocarrier systems, aiming to deliver drugs to target specific tumor sites with high spatial and temporal control over drug release. These systems mainly utilize nonionizing radiation and are primarily composed of biodegradable polymers. The physicochemical approaches that endow nanocarriers with photoresponsivity are categorized into three different classes: (1) photochemically-triggered, where the absorbed light energy is enough to simply break up covalent bonds or through a photochemical reaction, (2) photoisomerization, where the excess energy induces structural changes, and (3) photothermal, where the absorbed photon energy is dissipated *via* vibrational motion. Liposomes are popular nanocarriers used in encapsulating both hydrophilic and lipophilic drugs for targeted delivery. Liposomes are considered as one of the healthiest, safest, and most effective nanocarriers developed so far. They are composed of naturally-occurring substances that can be easily metabolized inside the human body, so they can be regarded as biodegradable, biocompatible, safe and non-toxic drug vehicles [152]. Recent advances in liposomal drug delivery comprise: (1) long-circulating (sterically-stabilized), (2) remote loading of drugs into liposomes by a pH and ion (ammonium or acetate) gradients, and (3) lipoplexes by the interaction of anionic nucleic acids or proteins with the surface of cationic liposomes [153,154]. These advances encompass the improvement of drug loading capacity and encapsulation efficiency, as well as the enhancement of drug pharmacokinetics, biodistribution, therapeutic efficacy, and reduction of systemic side effects and toxicity. Liposomes are capable of targeted, specific-modification and stimuli-responsiveness, which make them more effective in cancer treatment. Liposomes and their flexibility for surface modification by the addition of targeting moieties make liposomes more promising candidates. Targeting ligands surface-modified liposomes are often combined with different stimuli for better localized delivery and chemotherapeutic release with minimal systemic exposure and reduced toxicity. The progress from single-function to multifunctional-responsive liposomes has demonstrated huge therapeutic potential for targeted cancer therapy. The development of multifunctional liposomes with light-responsive property sheds light on highly efficient combined cancer therapy.

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Abbreviation

Abbreviation	Definition
ABC	Accelerated blood clearance
ALA	5-aminolevulinic acid
Azo SM	N-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-D-erythro-sphingosylphosphorylcholine
BHA	4-butylazobenzene-4-hexyloxy-trimethyl-ammoniumtrifluoro-acetate
BHA-cur-lipo	BHA-curcumin-liposomes
Bhc	6-bromo-7-hydroxy-4-hydroxycoumarin
BTSL	Bubble-generating thermosensitive liposomes
CHEMS	Cholesteryl hemisuccinate
CJM-Chol	CJM126 mixed with cholesterol derivative
CMA	7-(2-methacryloyloxyethoxy)-4-methylcoumarin
CMC value	Critical micelle concertation value
P(MEOMA-co-CMA)	Coumarin-containing poly(2-(2- methoxyethoxy)ethyl methacrylate)
CPT	Chemophototherapy
CTX	Cabazitaxel
CTX-PoP-Lip	Cabazitaxel-loaded porphyrin-phospholipid liposomes
CuAAC	Copper-catalyzed azide alkyne cyclo-addition
DNQ	2-diazo-1,2-naphthoquinone
DMPC	1,2-dimyristoyl-*sn*-glycero-3-phosphocholine
DMPG-Na	1,2-Dimyristoyl-*sn*-glycero-3-phosphoglycerol, sodium salt
DNA	Deoxyribonucleic acid
DOPC	1,2-Dioleoyl-*sn*-glycero-3-phosphocholine
DOPE	Dioleoyl-phosphatidylethanolamine
DOTMA	1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt)
DOTAP	1,2-dioleoyl-3-trimethylanmmonium-propane (chloride salt)
DPPC	1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine
DPPG-Na	1,2-Dipalmitoyl-*sn*-glycero-3-phosphoglycerol, sodium salt
DSPC	1,2-distearoyl-*sn*-glycero-3-phosphocholine
DSPE	1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine
DSPG-Na	1,2-Distearoyl-*sn*-glycero-3-phosphatidylglycerol, sodium salt
EE%	Percent encapsulation efficiency
EGFR	Epidermal growth factor receptor
EMA	European medicines agency
emc	Electronic medicines compendium
EPR	Enhanced permeability and retention
FDA	U.S. food and drug administration
FOE	Fiber optic endoscopy
FR	Folate receptor
GNOLs	Gold nanoshells coated oleanolic acid liposomes
HLB	Hydrophilic-lipophilic balance
HSPC	L-α-phosphatidylcholine, hydrogenated (soy)
ICG	Indocyanine green
IgM	Immunoglobulin M
IR	Infrared
LC%	Percentage of loading capacity
LUVs	Large unilamellar vesicles
MAA	Methacrylic acid
mAbs	Monoclonal antibodies
MAL	Methyl aminolevulinate

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MC	Merocyanine
MEO_2MA	2-(2-methoxyethoxy)ethyl methacrylate
MLVs	Multilamellar large vesicles
MPEG-2000-DPPE-Na	*n*-(methoxypolyethylene glycol 2000 carbamoyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylethanolamine, monosodium salt
MPEG-5000-DPPE-Na	*n*-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylethanolamine, monosodium salt
MPS	Mononuclear phagocyte systems
m-THPC	Meta-tetrahydroxy phenyl cholorin
NIR	Near-infrared
ONB	o-nitrobenzyl
PC	Phosphatidylcholine
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PEG-PLEA	Poly(ethylene glycol)-poly(lactic acid-ethanolic acid)
PEG-PMI-DTE	PEGylated perylenemonoimide-dithienylethene
PEO	Polyethylene oxide
PET	Photo-induced electron transfer
PIT	Photoimmunotherapy
Pheo-a	Pheophorbide-a
PNB	Poly (4,5-dimethoxy-2-nitrobenzyl methacrylate
POPC	1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine
PTT	Photothermal therapy
RES	Reticuloendothelial system
ROS	Reactive oxygen species
$SC\text{-}CO_2$	Supercritical carbon dioxide
SP	Spiropyran
SPR	Surface plasmon resonance
SP-to-MC	Spiropyran-to-merocyanine
SPTPC	Spiropyran-containing triazole-phosphatidylcholine
SUVs	Small unilamellar vesicles
TFR	Transferrin receptor
TPA	Two-photon absorption
TPC	Triazole-phosphatidylcholine
TTA	Triplet–triplet annihilation
UCNPs	Upconverting nanoparticles
uPA	Urokinase-plasminogen activator
UV	Ultraviolet
VPTT	Volume-phase transition temperature
$^1O_2$	Singlet oxygen
$^3O_2$	Molecular oxygen
18:0-Azo PC	1-stearoyl-2-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-*sn*-glycero-3-phosphocholine (CAS No.: 2098674-45-2)
18:0-PhoDAG	1-stearoyl-2-[(E)-4-(4-((4-butylphenyl)diazenyl)phenyl)butanoyl]-*sn*-glycerol

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