Journal of Innovative Technology, Vol. 8, No. 2, pp. 137-149, September 2026
http://doi.org/10.29424/JIT.202609_8(2).0011

Targeting Approaches For Treatment Of Cancer Using Liposomes

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ABSTRACT

In recent years, nanocarrier-based drug delivery has advanced significantly for the therapy of various cancer types. Among different nanocarriers, liposomal nanotechnology has attracted remarkable scientific attention. Liposomal encapsulation is the most effective approach for enhancing the therapeutic index compared to conventional anti-cancer formulations. This approach allows the drug to accumulate preferentially within the tumor site, maximizing its efficacy while minimizing its toxicity. Liposomes exhibit several notable characteristics over conventional drug delivery systems, such as improved therapeutic profile, high biocompatibility and biodegradability, low toxicity, targeted profile, and sustained drug release. The delivery of drugs through liposomes is endowed with distinct molecular and structural versatility. This diversity includes PEGylated stealth liposomes, stimuli-responsive liposomes, and various ligand-functionalized liposomes. This targeting behavior is based on both passive (responsive to endogenous or exogenous stimuli, e.g., redox, temperature, pH, ultrasound, light) and active targeting (receptor-mediated targeting through conjugated liposomes). This review illustrates the biophysical properties and compositional analysis of liposomal carriers, outlining the convenient choice of mechanisms of drug targeting for a particular cancer. Furthermore, it also surveys examples of targeting drugs from preclinical investigations to advanced clinical studies. Collectively, the analysis opens up novel possibilities to furnish a conceptual framework that may help to boost up the rational design of novel liposomal drug delivery platforms, ultimately expanding the therapeutic armamentarium against malignant disease. This review provides a comparative evaluation of liposomal targeting strategies while integrating the key translational challenges that influence their clinical applicability. Particular emphasis is placed on PEG immunogenicity, accelerated blood clearance, complement activation-related pseudoallergy (CARPA), and manufacturing scalability, highlighting how these factors can determine the successful translation of liposomal designs from laboratory development to clinical application.

Keywords: Targeted drug delivery, liposomes, active targeting, passive targeting, Cancer, Nanoparticles

1. INTRODUCTION

Cancer ranks as one of the leading causes of death in humans; thus, cancer treatment continues to be the prominent focus of research [1, 2]. Normally, cell death occurs as a physiological process during which information is received by the cells to die, so that the body can replace them with newer functional cells. Uncontrolled cell division and proliferation, combined with the loss of apoptotic mechanisms, cause cancer to progress dramatically ss[3]. Six major hallmarks set cancer cells apart from healthy cells and contribute to tumor development. It has been suggested that tumors comprise phenotypically diverse and functionally different neoplastic cells. Patient survival has increased lately owing to early-stage diagnosis, clinical trials, improved anticancer treatments, and advancements in adjuvant treatments [4, 5]. Radiotherapy, surgery, and chemotherapy have been the backbone of available cancer treatments around the globe. Chemotherapy is curative for advanced cancer types, including acute myelogenous lymphoblastic leukaemia, small-cell lung cancer, and germ cell cancer. Conventional tumor therapies, such as radiation and chemotherapy, have limited efficacy in treating tumors since their primary objective is to reduce the tumor burden [6-8]. Chemotherapy plays a vital role in cancer therapy, but faces a lot of challenges, such as poor targeting ability at the desired region and multidrug resistance (MDR). Angiogenesis inhibitor therapy is among the advanced treatments and is under development. Biological therapies, such as nanoparticles, interferons, vaccines, interleukin, and gene therapy, are also implied [9, 10]. Advanced research has shown that a type of cells referred to as cancer stem cells tend to act as a driving force for the majority of malignancies and resistance to therapies.

Cancer has been detected by the identification of several markers, including CEA, osteopontin, legumain, VEGP, and mesothelin. Over the years, various anti-cancer drugs have been developed that are capable of inhibiting tumor progression. While some drugs or compounds disrupt critical enzymes in the body, others may disrupt the way cells metabolize their nutrients. The same is true in their capacity to interrupt numerous vital cellu-

Manuscript received June 28, 2026; revised August 9, 2026; accepted August 30, 2026.

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lar activities, including drug resistance, DNA replication, DNA damage, programmed cell death, and apoptosis. These drugs have various mechanisms of action as well as selectivity for various cancer types [11-13]. DOX, containing an anthracycline moiety, is one of the most therapeutically active agents used to treat different tumors (leukemias, lymphomas, uterine, ovarian, and breast cancer).[16]. Despite its therapeutic efficacy, the drug is characterized by the presence of severe off-target effects (dose-limiting cardiac events, including cardiomyopathy, hepatotoxicity, haematological disorders), poor targeting efficacy towards tumors, and failure of therapy due to increased resistance issues are the obstacles that cause failure of therapy [18,19]. So, the challenge regarding use of these anthracycline therapies is to reduce the negative effects associated with chemotherapeutic agents without troubling the sensitive bio-environment and increase the therapeutic dose at the target site.

In order to curtail these limitations, many strategies have been developed, i.e., utilization of dose-modified prolonged infusions, formulating analogs of anthracyclines, co-administration of the drug with cardio-protective agents, and use of novel formulation techniques like nanotechnology utilizing various nano-carriers. Diagnostic and therapeutic drugs based on nanoscale and nanostructure have been developed, not just to treat cancer but also for its diagnosis and prevention [14-17]. Various nanocarriers such as liposomes, polymeric nanoparticles, mesoporous silica nanocarriers, nanoemulsions, and inorganic nanoparticles have been approved for the successful treatment of various cancerous diseases [14, 18-20]. A large number of colloidal systems are present in drug delivery, but liposomes are one of the most promising and widely accepted paradigms in the field of drug development that provide great advantages in cancer therapy, which can be demonstrated by the increasing number of commercialized liposomal drugs. Targeted therapy using liposomes as nanocarriers provides a promising strategy for addressing the drawbacks associated with conventional chemotherapy.

That said, none of this has solved every problem. The EPR effect that passive targeting relies on is notoriously inconsistent from one tumor to the next, and what looks reliable in a mouse xenograft rarely holds up as well once you move into human solid tumors [21]. PEGylation brings its own laggings too: repeated dosing can provoke anti-PEG antibodies that speed up clearance of the very liposomes meant to circulate for days. Add to this the practical difficulties of scaling up manufacturing, keeping batches consistent, and the limited amount of drug many liposomes can carry [22-24]. These issues are picked up in more detail later in this review [2].

2. LIPOSOMES AS NANOCARRIERS FOR CANCER TREATMENT

Liposomes are amphiphilic spherical self-closed nanostructures having size ranges from 50nm to 1000 nm, composed of a lipid bilayer and cholesterol (containing polar and non-polar components. It has been demonstrated through clinical studies that the agents entrapped in liposomes, acting as carriers, utilize various benefits, including:

- Improved biocompatibility, pharmacokinetic profile, and stability of therapeutic agent.
- Increased drug efficacy while reducing the toxicity profile.
- Protects the active agent from the harsh internal environment.
- Having an optimum loading capacity of both lipophilic and hydrophilic agents.
- Ideal porosity for drug release.
- Achievement for active targeting by making its interaction with specific ligands.
- Miniaturized carriers for diagnosis, screening, and delivery of cytotoxic drugs.
- Provide controlled drug release.
- Enabling it to make a smart delivery system by making it responsive to specific stimuli.
- Co-delivery of drugs or other therapeutic agents to provide better treatment of the required disease while overcoming the resistance issues at the same time.
- To provide spatiotemporal release of cytotoxic drug at the target site and to make its in vivo visualization by combining it with the imaging modalities [25].

Although various nanocarriers are being devised for efficient drug encapsulation and release, liposomal DOX formulations are among the first therapeutic nanocarriers that received FDA approval for their clinical efficacy and cancer treatment [26]. Liposome-based chemotherapeutics have been the focus of many studies, particularly for treating breast, bladder, ovarian, gastric, soft tissue sarcoma, lung, and Hodgkin's lymphoma [27]. Doxil is primarily used to treat ovarian cancer that might have recurred following platinum-based chemotherapy for Kaposi's sarcoma associated with AIDS [28, 29]. The most prominent feature of liposomal anthracycline DOX in cancer has been a decrease in many of the toxicities of anthracycline therapy rather than an increase in potency [30]. Hence, liposomal anthracyclines could be considered for inclusion in first-line or second-line regimens in place of standard anthracyclines.

With that gap in mind, Table 1 lines up the major classes of liposomal carriers covered in this review side by side, what each is good at, where it tends to fall short, and how far it has actually gotten in the clinic.

Table 1 Liposomal carrier types, compared by advantages, limitations, and clinical status.

Liposome Type	Key Advantages	Main Limitations	Representative Clinical Status	References
Conventional (non-PEGylated)	Biocompatible; encapsulates hydrophilic and lipophilic drugs; reduces off-target toxicity	Rapid opsonisation and RES clearance; short circulation half-life	Daunorubicin liposomal (DaunoXome®), approved	[31], [32]
PEGylated (stealth)	Prolonged circulation (up to ~55 h in humans); enhanced EPR-mediated accumulation	Anti-PEG IgM induction, ABC phenomenon, CARPA on repeated dosing	Doxil®/Caelyx®, FDA approved	[33], [34]

Liposome Type	Key Advantages	Main Limitations	Representative Clinical Status	References
Antibody-/ligand-targeted (immunoliposomes)	High target specificity; receptor-mediated cellular uptake	Complex, costly bioconjugation; possible ligand immunogenicity	Predominantly preclinical/early clinical trials	[35], [36], [37]
Folate- and peptide-targeted	Small, easily modifiable ligands; low production cost	Receptor expression heterogeneity between patients and tumors	Preclinical to early-phase clinical studies	[2], [38]
Aptamer-targeted	High affinity and specificity; low immunogenicity; easy synthesis	Nuclease susceptibility in vivo; limited long-term stability data	Predominantly preclinical	[39], [40]
pH-sensitive	Rapid, triggered release in the acidic tumor/endosomal microenvironment	Premature drug leakage during systemic circulation	Preclinical/early clinical	[41], [42]
Temperature-sensitive	Spatially and temporally controlled release via local hyperthermia	Requires precise, sustained local heating (40-43°C)	ThermoDox®, evaluated in Phase III trials	[43], [44]
Redox-sensitive	Selective release exploiting the elevated intracellular glutathione gradient	Formulation complexity; limited in vivo validation	Preclinical	[45]
Enzyme-sensitive	Exploits tumor-associated enzyme overexpression; potential for early metastasis targeting	Enzyme expression variability among tumors	Preclinical	[46], [47]
Magnetoliposomes	Combines drug delivery with MRI-traceable, magnetically guided targeting and hyperthermia	Long-term biodegradation/toxicity of iron oxide cores not fully defined	Preclinical/early investigational	[48]
Ultrasound-responsive (acoustically active)	Non-invasive, spatially precise, externally triggered release	Efficacy depends on tightly optimized acoustic parameters	Preclinical/early clinical	[49], [50]

3. LIPOSOMES TARGETING STRATEGIES

The two ways through which liposomes can be used for targeting cancerous cells include: passive targeting and active targeting [51, 52]. In passive targeting, EPR phenomena, i.e., enhanced permeability and retention, cause macromolecules, including liposomes, to accumulate primarily in the cancerous tissues. The EPR relies on the nanoparticles' size range in nanometers as well as two crucial features found in neoplastic tissues: impaired lymphatic drainage and leaky vasculature [53]. Passive strategy involves the use of <150 nanometers of particle-mediated EPR effects (which is specific to solid tumors). This physiological phenomenon is indicated by enhanced permeability of capillaries that surround solid tumors in comparison to normal tissues and the absence of functional lymphatic vessels. It allows nanoparticles within the blood to reach the site of the tumor either by passive diffusion or convection through the tumor's capillary pores. As a result, the nanoparticles accumulate in the tumor tissues, eventually making their way to the tumor mesenchyme as well as intracellular compartments. The notion of passively targeting different cancers with nanodrugs is based on this phenomenon [54].

Drug delivery systems based on liposomes for therapy of cancer have the potential to enhance the therapeutic effect of drug, via mechanism of passive targeting termed as the enhanced permeability and retention (EPR) effect in which concentration of drug remains higher specifically at the tumor site due to the presence of leaky vasculature at the tumor site which allows the liposomes to enter into the interstitial space as compared to healthy tissues and reduced lymphatic drainage force them to stay there for long time unless they are recognized by reticuloendothelial system (RES) [55]. This increased permeability of the vasculature in the tumor region is due to activation of certain pro-angiogenic molecules that result in increased fenestrations between the endothelial cells. Typically, the size of fenestrations may reach from 300 nm to 4,700 nm, depending upon the region of the tumor and hydrostatic pressure [56]. Also, lymphatic vessels are compressed due to increase number of cancerous cells. So, liposomes drained from the tumor vasculature and were retained for a longer time in the interstitial space as compared to normal organs [14]. In this way, a higher concentration of the drug reaches the target site than other normal host tissues and halts the systemic toxicity associated with the drug. Also, due to their excellent biocompatibility, easy adsorption, safety profile, and less toxicity, they are of great potential value. This is due to the protection provided by the phospholipid bilayer of liposomes that encapsulate the cytotoxic drug and thus protect healthy tissues from the unwanted effects of the drug. Figure 1 demonstrates the effect of EPR in cancer cells.

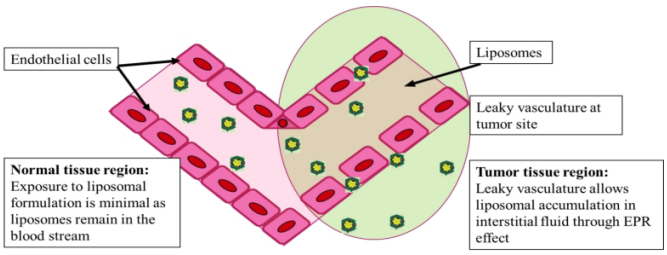


Fig. 1 The enhanced permeability and retention (EPR) effect. Tight endothelial junctions in normal tissue keep liposomes confined to the bloodstream, whereas the leaky, fenestrated vasculature characteristic of tumors allows liposomes to accumulate passively in the surrounding interstitial tissue.

One limitation is that EPR effect is the whole basis for passive targeting, yet how reliably it actually works in patients is genuinely contested. Mouse xenografts tend to show more uniform EPR effect than real human tumors do, where a dense extracellular matrix, high interstitial pressure, uneven blood vessel density, and plain patient-to-patient variability all get in the way of nanoparticle accumulation. So it is not surprising that EPR-dependent liposomes often accumulate in human tumors at levels well below what the animal data promised, and even when accumulation does occur, that alone does not guarantee a clinical benefit [21, 57]. This is one of the reasons that we started leaning more on combining passive accumulation with active, ligand-based targeting, or on strategies that try to boost the EPR effect itself, such as vascular normalization or image-guided delivery, instead of treating EPR as sufficient on its own.

However, the use of liposomal DOX is associated with poor penetration properties into the tumor tissues and is easily removed from the circulation through the reticuloendothelial system (RES), due to which a relatively large amount of drug needs to be administered. So by the use of pegylated liposomal formulations some of these issues can be circumvented.

4. PEGYLATED LIPOSOMES

In order to overcome the aforementioned limitations, different strategies are employed, leading to the development of "liposomes second generation". One of the foremost strategies described in the 1990s is PEGylation of the surface of liposomes, shown in Figure 2. PEGylated liposomes are rigid and small liposomes (~100 nm) with a polymeric coat made up of polyethylene glycol, which imparts various important attributes to the formulation [14]. PEGylation can be done through several ways, i.e., by adsorption of polymer onto the surface of liposomes, Incorporation of PEG-lipid during preparation of liposomes, and attachment of covalent reactive groups on preformed liposomal surfaces [58, 59].

The PEG polymer itself has several enchanting properties like biocompatibility, excellent solubility profile, low antigenicity and immunogenicity, reduced toxicity, and favorable excretion profile. These attributes allow the employment of PEG in various formulations for internal administration. These polymer-grafted preparations, by developing a protective, hydrophilic coating on their surfaces, protect the liposomal formulations from the attack of mononuclear phagocytic cells and have limited interactions with other body proteins, thus reducing adhesion to other cells and vessels and providing better stabilization effect. They may also be referred to as 'stealth' liposomes with enhanced steric stability due to their evasion from the immune system, which ultimately results in prolonged circulation time [60]. Also, the presence of PEG in the liposomal formulations inhibits aggregation of small particles, favoring the EPR effect of the formulation. The clinical findings of this process are evident by comparing the biodistribution and pharmacokinetics profile of conventional and stealth liposomes. Stealth liposomes display prolonged time of circulation, up to a time period of 55 hours in humans, and low clearance from blood. This ultimately results in several-folds improve drug concentration time in blood and plasma while mitigating the off-target effects associated with the conventional DOX, such as alopecia, cardiovascular events, and hematological disorders. Therefore, the clinically approved liposomal drug Doxil® is PEGylated to improve the limitations associated with the conventional formulation and is approved by the FDA. A clinical study also shows enhanced uptake and improved pharmacokinetic profile of PEGylated Liposomal DOX with improvement in clinical efficiency [26]. Also, less frequent administration and fewer toxicity interventions reduce the cost associated with pegylated liposomal formulations.

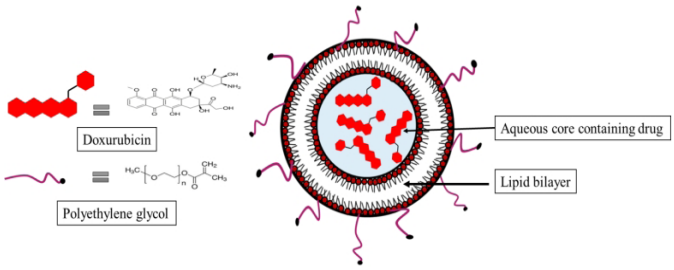


Fig. 2 Structure of a PEGylated (stealth) liposome. Doxorubicin is encapsulated within the aqueous core, while polyethylene glycol (PEG) chains grafted onto the lipid bilayer surface confer steric stabilization and prolong systemic circulation time.

It should be said, though, that PEGylated liposomes are not simply invisible to the immune system, as the term 'stealth' might suggest. Give a patient a repeat dose, and the body can raise anti-PEG IgM and IgG antibodies that latch onto the PEG shell of the next dose, setting off complement activation and clearing the liposomes from circulation far faster than intended, this is the accelerated blood clearance, or ABC, effect. In some patients that same complement activation shows up clinically as an acute hypersensitivity or infusion reaction, known as complement activation related pseudo allerggy CARPA [61]. Both effects work directly against what PEGylation is supposed to achieve, which is why more developers are now screening for anti-PEG immunogenicity and infusion-reaction risk early in preclinical and clinical development, rather than treating it as a rare edge case.

5. TUMOR TARGETED LIPOSOMES

Although stealth liposomal formulations are of great potential for the passive targeting of anthracycline moieties at the desired area, since these formulations are not directly targeted at the tumor region. Also, the specialized coatings made on the liposomal formulations sometimes inhibit their interaction with the tumor cells, and the liposomal formulation stays at the tumor region without the release of the drug. So, further development is

being made through direct interaction of cancerous cells with the liposomal formulations via the attachment of a specific ligand or antibody on their surfaces. So, stealth liposomes are further modified in terms of increasing selectivity by the attachment of specific ligands on their surfaces that encourage cellular uptake at the tumor site by receptors specific to endocytosis [62]. Active targeting refers to the modification of specific ligands, antibodies, or simply other molecules over the liposomal surface to identify and adhere to specific tissues or cells at the target site, resulting in more precise drug delivery. For example, antibody-adorned nanoparticles can recognize and bind to specific antigens located on the outer surface of tumor cells, allowing for precise targeted delivery of the drug. When nanoparticles are actively targeted in vivo, they follow an EPR effect and then proceed via a bypass pathway to the targeted tumor site with certain surface modifications. In 1980, the first demonstration of this phenomenon was proposed using antibodies grafted into the surface of liposomes, followed by numerous ligand types, such as peptides, aptamers, and nucleic acids. Immunoliposomes have gained much attention in clinical research in which an antibody is conjugated either directly to the liposomal head region, or attachment is made to the PEG polymer, or onto the surface of some other protein or polymer [63]. Also, DOX through liposomes can be delivered by selective targeting at folate receptors whose concentration is high at the tumor region.

5.1 Liposomes with antibody surface modification

The majority of studies conducted on actively targeted liposomes utilize antibodies to target different tumors [64]. The conjugation of anti-CD22 monoclonal antibodies to the pegylated DOX-loaded anti-CD22 monoclonal antibodies is conjugated to PEGylated DOX-loaded liposomes, which helps in the accumulation of DOX in case of non-Hodgkin's lymphoma with enhanced anti-cancerous activity and decreased toxicity profile [65].

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5.2 Liposomes with folic acid surface modification

Folic acid (a water-soluble analogue) is widely utilized in modern research to target diseases, including Cancer, Rheumatoid arthritis [66]. FA binds selectively with the receptors that are highly expressed in the Folate receptors. These FR are hardly expressed in normal cells; however, certain lung, colon, brain, ovarian, breast, and kidney tumors indicate overexpression of the FR [67]. FR-α is highly expressed in epithelial cancers, while FR-β is overly expressed on the surfaces of macrophages. Liposomes modified with Folic acid help to deliver the drug, genes, radionuclides, and other therapeutic moieties to the cancer cells that are highly expressed with folate receptors and demonstrate receptor-mediated endocytosis. Riviere et al. showed that folate-targeted DOX liposomes could improve in vivo drug delivery for KB tumor treatment in mice [67]. PEGylated liposomes conjugated with folic acid display an increased antitumor efficacy due to longer circulating half-life and increased drug solubility.

5.3 Liposomes with peptide surface modification

Peptide-mediated liposomes have been widely employed for delivering anticancer drugs as well as siRNA owing to their benefits. Since they have a small structure and are more modifiable than antibodies, they can be chemically synthesised more easily to achieve the desired targeting. In recent years, phage display libraries have been studied to enable peptide-mediated liposomal delivery of drugs by improving the targeting of nanocarriers [68]. LHRH receptors are overexpressed in various cancers, including prostate, breast, and ovarian cancerous cells, but the majority of visceral organs lack these receptors. Research demonstrated that pegylated liposomes conjugated with LHRH peptides, loaded with paclitaxel, increase the drug at the tumor site with better anti-cancerous activity, thereby significantly reducing the unwanted side effects in comparison to the non-targeted liposomes [69].

5.4 Liposomes with aptamer surface modification

Aptamers are single-stranded, three-dimensional DNA or RNA that bind to specific target cells, including various protein receptors. Aptamers are successful innovative markers that are applied for targeting cancerous biomarkers. They served as effective ligands for the delivery of various anti-cancerous agents [70]. The intrinsic advantages of aptamers include biocompatibility, high programmability, easy synthesis, and convenient modification Dihua et al. synthesized sgc8 (nucleic acid aptamer) for the precise recognition of the acute lymphatic cells with leukemia [71]. In an effort to determine whether the IL-4Rα-liposome (CpG ODN) delivery system could deliver CpG into tumor masses as well as overcome the immunosuppressive TME, Liu et al. identified that, when CT26 tumor-carrier mice were treated with IL-4Rα-liposome-CpG therapy, the antitumor activity was significantly higher than in the control group [72].

Putting these four ligand strategies side by side, it becomes clear they are not interchangeable. Antibody-based immunoliposomes usually win on specificity and affinity, but that comes at a price: expensive to produce, the antibody itself can provoke an immune response, and the conjugation chemistry is complicated enough that most of these constructs are still stuck at the preclinical or early-clinical stage. Folate- and peptide-based ligands are a cheaper, simpler alternative to make and modify, though how well they work clinically depends a lot on whether the target receptor is actually expressed consistently across patients and tumor types, which is not something you can count on. Aptamers sit somewhere in between: high affinity, low immunogenicity, and easy chemical synthesis, but they get degraded by nucleases in vivo, and there is simply less long-term safety data behind them compared with antibodies or peptides. Table 2 lays these strategies out together with their mechanisms, example ligands, advantages, limitations, and how far each has progressed clinically.

Table 2 Comparative summary of active (ligand-mediated) liposomal targeting strategies.

Targeting Strategy	Mechanism	Representative Ligands/ Examples	Advantages	Limitations	Clinical Stage	Reference
Antibody-mediated (immunoliposomes)	Receptor-mediated endocytosis via surface-conjugated antibody/fragment	Anti-CD22 mAb; milatuzumab (anti-CD74); HER-2-targeted antibodies.	High specificity and affinity.	High cost; complex bioconjugation; possible immunogenicity.	Preclinical-early clinical	[73]
Folate receptor-mediated	Receptor-mediated endocytosis via folate receptor (FR) overexpression	Folic acid-conjugated liposomal DOX	Low cost; easy synthesis; high FR affinity	Heterogeneous FR expression across tumors/patients	Preclinical-early clinical	[74]
Peptide-mediated	Receptor-mediated endocytosis via peptide-receptor recognition (e.g., LHRH)	LHRH-peptide-paclitaxel liposomes	Small size; easily modifiable; low immunogenicity	Lower affinity than antibodies; proteolytic degradation	Preclinical-early clinical	[75]
Aptamer-mediated	High-affinity binding of ssDNA/ RNA aptamer to tumor biomarker	sgc8 aptamer; IL-4Rα aptamer-CpG liposomes	High affinity; low immunogenicity; easy chemical synthesis	Nuclease susceptibility; limited long-term stability data	Preclinical	[76]

6. STIMULI SENSITIVE LIPOSOMES

In order to get an additional level of intended therapeutic effect and a high level of sophistication, another approach for the release of the drug specifically at the tumor area is by coupling the liposomal formulation to a specific stimulus. A multifunctional approach is utilized by the coupling of stimuli-sensitive formulations with the long-circulating targeted liposomal formulations. The principle behind this strategy is that certain stimuli, that is, whether the intrinsic characteristics of the pathological site or applied from the external source to the targeted area, are used to trigger the release of the drug from the formulation, providing controlled release of the drug, the drug fate inside the body, and modifying the behavior of the liposomal formulation at the cellular target. These liposomes contain specialized lipids as triggerable agents to modify their stability and permeability characteristics. These liposomes have the ability to release the drug only after being triggered by specific stimuli [77].

The stimuli that are commonly utilized to modify behavior of liposomal formulations can be internal according to the physiological and pathological stimuli of the tumor region such as change in pH, the activity of specific chemicals or enzymes, change in redox potential, temperature sensitive (which can be local or can be increased from outside source) or it can be typical external stimuli that can be provided from outside of the body i.e., magnetic field triggered, ultrasound or through various types of irradiations [78].

Endogenous and exogenous stimuli each come with a genuine trade-off. Endogenous stimuli, pH, redox potential, enzyme activity, are convenient in that release happens on its own once the liposome reaches the tumor, no extra equipment needed, but they only work as well as the underlying pathology is consistent, and that can vary quite a bit between patients, or even between regions of the same tumor. Exogenous stimuli like heat, magnetic fields, and ultrasound give clinicians far more control over exactly when and where the drug is released, and can be paired with imaging to watch it happen in real time, but that control comes at the cost of needing dedicated equipment, careful dosimetry, and delivery in a specialized clinical setting, not something every hospital can offer.

7. DRUG RELEASE BY PATHOLOGICAL TUMOR- ENVIRONMENTAL STIMULI

Under this approach, liposomes are developed to respond to internal tumor stimuli and release the drug in response to changes in the tumor microenvironment.

7.1 pH Sensitive Liposomes

Development of pH-sensitive liposomes is an amicable strategy to accumulate cytotoxic drugs in the desired area. As pH variations are present in the tumor region, which is considered more acidic due to increased metabolic acidosis and hypoxia due to increased cell death in the tumor area (pH < 7) [79]. In addition, the lysosomal and endosomal regions in the tumor area are more acidic than the intracellular space, having a pH range

of 5 to 6.2 due to ATP-mediated accumulation of protons. This change of pH gradient is utilized for the liposomal formulations that are designed to release the therapeutic moiety where pH is low. Different strategies have been utilized for making liposomal formulations pH sensitive, i.e., by use of compounds that contain acidic groups (remain stable at neutral pH by acting as a stabilizer), through use of synthetic fusogenic peptides, or by utilization of pH-sensitive polymers or lipids in the formulation containing pH-sensitive acetal, hydrazone, or cis-acotinyl linkages. Inclusion of such pH-sensitive compounds imparts the characteristics of fusogenic properties in them because of their transition or destabilization either through the biological membranes (endosomal or plasma membranes) or in their absence, followed by the release of encapsulated drug [80]. Figure 3 shows the mechanism of drug release from this type of liposome. Various studies have shown that a pH-sensitive liposomal formulation of DOX increases its therapeutic activity and accumulation in the target region. Stealth pH-sensitive liposomes for Hyaluronic Acid receptor targeting have been developed for DOX which releases the drug faster in areas where there is acidic pH (nearly pH 5) and can effectively be utilized for the treatment of solid tumors. Also, combination strategies of pH sensitivity and attachment of ligands for more targeted delivery in specialized areas have been devised in order to gain better therapeutic effects [79].

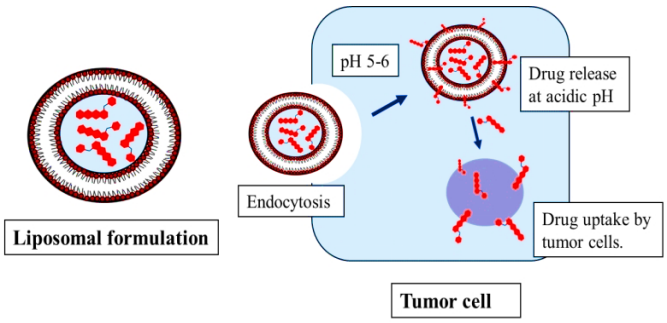


Fig. 3 pH-triggered drug release from pH-sensitive liposomes. Following cellular uptake by endocytosis, the acidic tumor and endosomal environment (pH 5-6) destabilizes the liposomal membrane, triggering drug release and subsequent uptake by tumor cells.

One problem that keeps coming up with pH-sensitive liposomes is premature leakage in the bloodstream. Blood sits at around pH 7.4, which is not that far off from the tumor interstitium or early endosomes, so a formulation tuned to be too responsive to small pH shifts can end up releasing its payload before it ever reaches the tumor, which defeats the purpose and adds unnecessary toxicity risk. Getting the balance right, stable enough at physiological pH but still quick to release once it hits tumor or endosomal pH, takes careful tuning of the lipid or polymer composition, and it remains one of the harder formulation problems standing in the way of this approach reaching the clinic.

7.2 Temperature Sensitive Liposomes

In this strategy, the release of cytotoxic drugs at the target site is accomplished by the use of thermosensitive liposomes in a controllable fashion. Most of the pathological sites, like tumor regions, are naturally hyperthermic] or consequent local heating of the tumor can be maintained from an external source that ultimately helps to increase blood flow and increase the fenestrations between the endothelial cells, which promotes extravasation of liposomes at the required area, encouraging passive perfusion of the liposomal formulation [81]. Studies have shown that this local hyperthermia has triggered the release of the liposomal formulation, as shown in Figure 4.

Keeping a tumor steady within a 40-43°C window for long enough is harder in practice. It takes real-time temperature monitoring and carefully controlled heat delivery, focused ultrasound, radiofrequency, or microwave hyperthermia, and getting it wrong in either direction is a problem: too little heat and the drug never releases properly; too much and healthy tissue nearby can be damaged. That need for specialized equipment and trained staff, combined with how much tumor depth and blood supply can vary from patient to patient, is a big part of why temperature-sensitive liposomes have not become routine despite some genuinely promising trial results.

In order to ensure release of the drug in a controllable fashion, constant maintenance of temperature (40–43 °C) is considered as the main factor for achieving the desired outcome. For the preparation of such liposomal formulations, suitable lipids with the desired characteristics of gel-to-liquid phase transition are required, i.e., lysolipids or dipalmitoylphosphatidylcholine [82]. ThermoDox is a temperature-sensitive lysolipid liposomal formulation of Dox. Through recent research, it is demonstrated that encapsulation of Dox in cationic thermosensitive liposomes exhibits increased efficacy and potential for the release of cytotoxic drug at the tumor site [83].

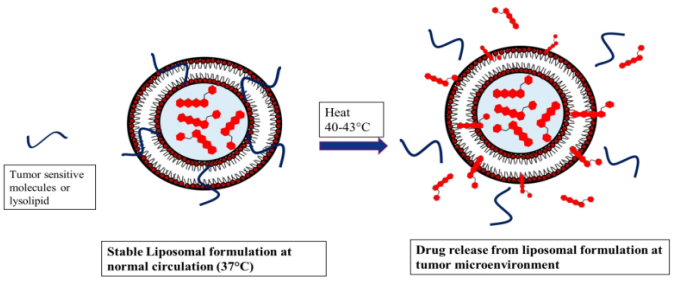


Fig. 4 Temperature-triggered drug release from thermosensitive liposomes. The formulation remains stable at normal body temperature (37°C) but undergoes a lipid phase transition on localized heating to 40-43°C, releasing the encapsulated drug at the tumor site.

7.3 Redox Sensitive Liposomes

It is one of the potential approaches that utilizes the difference of redox potential between cancerous and normal cells or in extracellular and intracellular regions. For instance, it is a known fact that the concentration of reducing agents is higher (4-fold) in tumor areas as compared to normal tissues, and glutathione concentration is 100-1000-fold higher in cancerous tissues than in the blood, and also it is mildly reducing in the intracellular region i.e., approximately 2–10 mM, and oxidizing at the extracellular region i.e. approximately 2–20 μM. Based on this strategy, redox-sensitive liposomes have found great potential for the selective release of cytotoxic drugs at the desired region, i.e., tumor cells [84]. These redox-sensitive liposomes contain disulfide bonds as cleavable linkers on their surfaces. Cleavage or reduction of these bonds to thiol groups results in the removal of the hydrophilic group, followed by membrane destruction and release of the

drug at the cancerous site. So, the liposomes remain stable at the sites where the concentration of GSH is low, but rapidly deform at the sites where there is a reducing intracellular region. Recently, a redox-sensitive formulation of anthracycline DOX has been prepared that showed excellent stability at physiological conditions and released the drug after sensing glutathione concentration of 10 mM. This formulation is considered superior to Doxil and Caelyx.

7.4 Enzymes Sensitive Liposomes

A relatively novel method to deliver the drug to the tumor site is to target the enzymatic activity of the desired region. Overexpression of certain tumor-associated enzymes is utilized as a biomarker and is considered an internal stimulus for the release of active ingredients in the tumor area, where their concentration is high [85]. Several enzyme levels are increased in cancerous regions, i.e., proteases, MMPs, and phospholipases, and are exploited as the triggering molecules for the release of the drug from the liposomal formulation. Such liposomal formulations will remain stable in the blood circulation and, after being accumulated at the tumor site through extravasation, further need to release the drug at the intracellular compartment of the tumor region by the activity of fusogenicity of the design formulation after being triggered by the specific enzymes [86]. It is an interesting approach for delivering desired drug to the affected area and also provides potential to target the metastatic tissues at an early stage. Often, this strategy is combined with other releasing mechanisms in order to improve drug accumulation in the tumor.

8. DRUG RELEASE BY EXTERNAL PHYSICAL STIMULI

8.1 Magneto Liposomes

It is a versatile drug delivery system in which magnetic nanoparticles are encapsulated in the liposomal formulations, or they can be made magnetized by the modification of magnetic metal particles with suitable biocompatible polymers, as depicted in Figure 5. As compared to other stimulus-responsive delivery systems, this strategy show combines benefits of visualization through magnetic resonance imaging and selective targeting of the formulation under the influence of an external magnetic field [87, 88]. Iron oxide nanoparticles, i.e., magnetite (Fe3O4) and maghemite (Fe2O3), with a size of 4–10 nm, are most commonly employed due to their small size and superparamagnetic properties. They are most commonly referred to as ‘superparamagnetic iron oxide nanoparticles’ [89]. This strategy has great potential in cancer therapy by combining drug delivery specifically at the cancer site and the production of a local hyperthermic effect, which causes the death of cancerous cells. After intravascular injection of these magneto-liposomes, they are transported through the blood circulation and finally accumulate and are targeted to the tumor site through the external application of an alternating magnetic field. The stray effect of the magnetic field can be lessened by making nanoparticles of less than 10nm of ferromagnetic substances. These magnetic liposomes can then further be used as MRI (magnetic resonance imaging) contrast agents, and their in vivo biodistribution can also be monitored [90]. Several studies show improved accumulation of DOX at target sites guided through an external magnetic field. Recently, magnetic liposomes of DOX have been prepared for their controlled release using thermosensitive techniques, providing efficacious release of the drug at the target site.

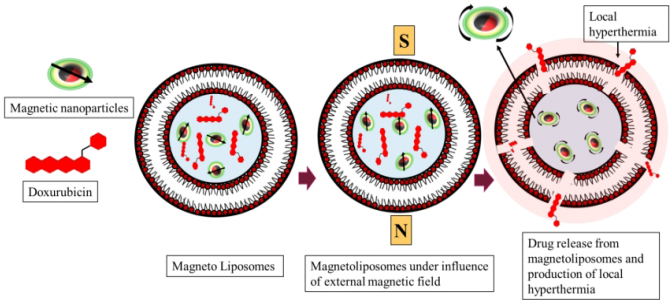


Fig. 5 Magnetically guided drug release from magnetoliposomes. Embedded magnetic nanoparticles enable liposome accumulation under an external magnetic field (S/N poles); exposure to an alternating magnetic field then generates local hyperthermia and triggers drug release at the tumor site.

Magnetoliposomes are appealing precisely because they combine drug delivery, imaging, and hyperthermia, but the long-term safety picture is still fairly incomplete. Questions remain about how quickly the iron oxide cores actually degrade and clear from the body, whether the free iron released along the way causes oxidative stress, and what repeated exposure to alternating magnetic fields does over time, none of which has been pinned down with the kind of systematic toxicology work needed before this strategy can move much past early-stage trials.

8.2 Ultrasound-Sensitive Liposomes (Acoustically Active Liposomes)

In this strategy, externally ultrasonic waves are directed in order to monitor the release profile from liposomal formulations. The general principle is based on the drug delivery system that, after accumulation at the target site, liposomes are allowed to release the drug in a controlled fashion by application of ultrasonic waves. The technique has found special interest for targeted release of drugs as the ultrasonic waves can penetrate easily into the body’s interior and can be focused on the desired tumor site [91]. Acoustically active liposomes are initially formulated as ultrasound contrast agents and contain a small amount of gas (air) or perfluorated hydrocarbons, which can be loaded with the active ingredient that is allowed to be released at the tumor site after damaging its surface through application of ultrasound, as shown in Figure 6. The release behavior of liposomal formulations depends on the energy and frequency of ultrasonic waves, as well as on the composition of phospholipid bilayers [92]. Also, it influences the mechanism of drug release, i.e., thermal or mechanical. Through research, it has been demonstrated that ultrasonic waves at high frequencies can damage the surface of liposomes through thermally induced changes and results in phase transition from gel to liquid by increasing phospholipids mobility triggering the release of drug and the ultrasonic waves at low frequency promotes alteration of lipids mechanically, that creates structural defects in the liposomal structures and membrane rupture stimulating the release of drug at the tumor site. Mostly, a combination strategy for making liposomal formulations is employed for the controlled release of the drug at the tumor site. A study demonstrates effective release of liposomal anthracycline DOX from temperature-sensitive liposomes on exposure to high-frequency ultrasonic waves and evaluated under magnetic resonance imaging [93]. Also, high-intensity ultrasound

application through temperature-sensitive liposomes under MR guidance in a rabbit model evaluates the clinical translation of DOX in solid tumors.

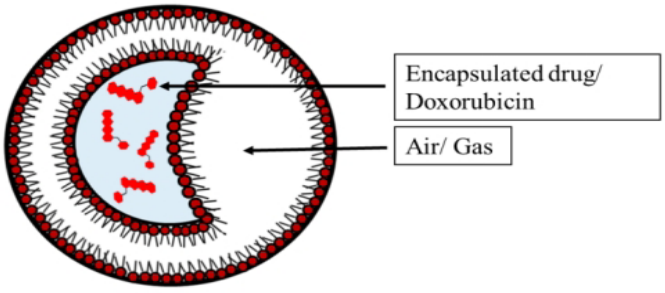


Fig. 6 Structure of an acoustically active (ultrasound-responsive) liposome. A gas/air core alongside the encapsulated drug enables ultrasound-induced cavitation, which disrupts the lipid bilayer and releases the drug upon exposure to focused ultrasound.

How well ultrasound-responsive liposomes actually work depends on getting the acoustic settings right, frequency, intensity, duty cycle, exposure time, and these need to be tuned separately for each part of the body, because the same parameters that trigger drug release can also cause unwanted mechanical or thermal damage if not well controlled. Standardizing ultrasound dosimetry and pairing it with real-time imaging guidance is still very much a work in progress, but it is probably necessary before the safety and efficacy seen in preclinical models can be counted on to carry over into the clinic.

9. CHALLENGES AND TRANSLATIONAL BARRIERS IN LIPOSOMAL DRUG DELIVERY

Setting aside the issues specific to each strategy above, there are a handful of recurring problems that shape whether liposomal drug delivery systems in general make it to the clinic.

9.1 PEG immunogenicity, ABC, and CARPA

As already discussed in Section 4, PEGylation cuts both ways: essential for keeping liposomes in circulation, but capable of triggering anti-PEG antibodies that speed up clearance on repeat dosing (the ABC phenomenon) and, in some patients, complement-related infusion reactions (CARPA). How much this happens depends on the dose, the specific formulation, and the interval between doses, and that unpredictability is still a genuine obstacle when designing regimens that call for repeated administration [94].

9.2 Manufacturing scalability and reproducibility

Methods that work fine on the lab bench, thin-film hydration, sonication, extrusion, do not always scale up cleanly to Good Manufacturing Practice (GMP)-compliant production; particle size, polydispersity, and how much drug actually gets encapsulated can all shift once volumes increase [95]. Add in batch-to-batch inconsistency, the cost and fuss of sterile-filtering nanoscale vesicles, and the fact that continuous, scalable platforms such as microfluidics or cross-flow injection are still not widely available, and it depicts why relatively few liposomal candidates make their journey from bench to clinic [96].

Drug-loading limitations

How much drug a liposome can actually carry is limited, and that limit depends on the drug's lipophilicity, whether it has an ionizable group that active-loading gradients can exploit, and how stable the drug-lipid interaction turns out to be. Poorly soluble or weakly ionizable drugs tend to load inefficiently, and whatever does get loaded can leak back out during storage or while circulating, chipping away at the dose that actually reaches the tumor. Improving loading efficiency without sacrificing stability is still an active problem rather than a solved one [97].

Clinical trials, regulatory status, and approved liposomal formulations

A handful of liposomal anticancer formulations have already made it through clinical development to regulatory approval, which is proof the underlying strategies can work in practice, though many others discussed in this review are still sitting at earlier, preclinical or early-clinical stages, as shown in Table 3.

Table 3 Where liposomal anticancer formulations currently stand? Regulatory and clinical trial status.

Formulation	Liposome Type	Indication	Regulatory/Trial Status	References
Doxil®/Caelyx® (pegylated liposomal doxorubicin)	PEGylated (stealth)	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	FDA approved	[98]
DaunoXome® (liposomal daunorubicin)	Conventional	HIV-associated Kaposi's sarcoma	FDA approved	[98]
Myocet® (non-PEGylated liposomal doxorubicin)	Conventional	Metastatic breast cancer (combination therapy)	Approved (EU; regional approvals)	[99]
Onivyde® (liposomal irinotecan)	PEGylated	Metastatic pancreatic adenocarcinoma	FDA approved	[100]

Formulation	Liposome Type	Indication	Regulatory/Trial Status	References
Vyxeos® (liposomal daunorubicin/cytarabine)	Conventional (dual-drug co-encapsulation)	Therapy-related AML / AML with MDS-related changes	FDA approved	[101]
Marqibo® (liposomal vincristine)	Conventional	Philadelphia chromosome-negative ALL	FDA approved	[102]
ThermoDox® (thermosensitive liposomal doxorubicin)	Temperature-sensitive	Hepatocellular carcinoma (with radiofrequency ablation)	Evaluated in Phase III trials	[103]
Ligand- and aptamer-targeted liposomal DOX formulations	Active-targeted (folate/peptide/aptamer)	Various solid tumors (investigational)	Preclinical to early-phase clinical	[104]

Passive, EPR-dependent and PEGylated liposomes have already delivered real clinical impact, while the actively targeted and stimuli-responsive designs are mostly still preclinical or early-stage. That gap is not really about the underlying science being weaker, it reflects the extra manufacturing, regulatory, and safety hurdles that come with a more complicated, multifunctional formulation.

10. CONCLUSION

Liposomes have come a long way from an interesting idea to an actual clinical tool, and several PEGylated and conventional formulations are now standard parts of oncology practice. What this review has tried to make clear, though, is that not all liposomal targeting strategies are equally ready for prime time. As Tables 1-3 show, they differ considerably in how well they target tumors, how hard they are to manufacture, how safe they are, and how far along the clinical pipeline they are. Passive targeting on its own looks less sufficient once you account for how variable the EPR effect really is in human tumors, and PEGylation, for all its pharmacokinetic benefits, brings its own immunogenicity baggage in the form of ABC and CARPA. Where does this leave the field? A few things stand out. Tumor delivery could be made more predictable on a patient-by-patient basis by combining passive accumulation with active, ligand-based targeting and strategies that boost the EPR effect itself. Manufacturing also needs real investment: microfluidic and continuous-flow production that can scale and stay reproducible, so promising formulations don't stall at the preclinical stage. And newer platforms such as magnetoliposomes and stimuli-responsive systems still need the long-term safety and biodegradation work that would let them move further into trials. Getting there will take more than minor adjustments to existing formulations. It will take combining these strategies deliberately if liposomal nanocarriers are going to live up to their potential against cancer.

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