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Review

The modification of conventional liposomes for targeted antimicrobial delivery to treat infectious diseases

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Abstract
Some of the most crucial turning points in the treatment strategies for some major infectious diseases including AIDS, malaria, and TB, have been reached with the introduction of antimicrobials and vaccines. Drug resistance and poor effectiveness are key limitations that need to be overcome. Conventional liposomes have been explored as a delivery system for infectious diseases bioactives to treat infectious diseases to provide an efficient approach to maximize the therapeutic outcomes, drug stability, targetability, to reduce the side-effects of antimicrobials, and enhance vaccine performance where necessary. However, as the pathological understanding of infectious diseases become more known, the need for more advanced liposomal technologies was born to continue having a profound effect on targeted chemotherapy for infectious diseases. This review therefore provides a concise incursion into the most recent and vogue liposomal formulations used to treat infectious diseases. An appraisal of immunological, stimuli-responsive, biomimetic and functionalized liposomes and other novel modifications to conventional liposomes is assimilated in sync with mutations of resistant pathogens.

Keywords Liposomes · Delivery system · Antimicrobials · Infectious diseases · Encapsulation · Targeted delivery

1 Introduction

Infectious diseases remain a global health concern perpetuated by different harmful microorganisms (bacteria, fungi, viruses, and parasites) [1]. These microorganisms traverse between individuals via vector-borne transmission, air droplets, zoonoses, and direct body contact [1, 2]. Vaccines and antimicrobials are the gold standard to treat and manage infectious diseases. Several promising vaccines have entered clinical trials against HIV and Malaria but none to date are clinically available [3]. Meanwhile, a *Mycobacterium tuberculosis* (Mtb) vaccine, based on neonatal BCG immunization, is unable to prevent Mtb transmission in adults and adolescents [4]. Even though antimicrobials have demonstrated efficacy to treat infectious diseases, there remains drawbacks to current treatment regimens, such as rising antimicrobial drug resistance, low efficacy, significant side-effects, patient non-compliance, poor tolerability, and restricted access to medicines due to various factors [1, 5].

The design of new antimicrobial drugs largely for low-middle income countries (LMICs) that are mostly burdened by infectious diseases is also hampered by the reduced profitability for most antimicrobial drug discovery programs to balance the complexity of using conventional approaches and the expectation that these too will ultimately develop

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resistance. This burden is compounded by the regulatory requirements that demand extensive and intricate clinical trials before antimicrobials can be approved [6]. Thus, much attention has focused on new strategies to prevent the cycle of resistance in pathogens and not only the discovery of new antimicrobials [1, 7].

One approach is the use of patient-centric nano-liposomes (NLs) designed to overcome the limitations of current antimicrobial chemotherapy. NLs (Fig. 1), are synthetic nano-colloids that can transform the fate of infectious diseases by maximizing antimicrobial efficacy and reduce side-effects by encapsulation within NL [7, 8]. Among its primary advantages is therapeutic stability, improved bioavailability, and site-specific or target antimicrobial transport to minimize drug resistance. In addition, NLs can regulate immune system interactions against pathogens with the flexibility to co-deliver antimicrobials with immunomodulators to achieve host-directed therapy (HDT) [9, 10]. This multifunctional approach also addresses the challenge of treating infections caused by multidrug-resistant (MDR) pathogens [9, 11].

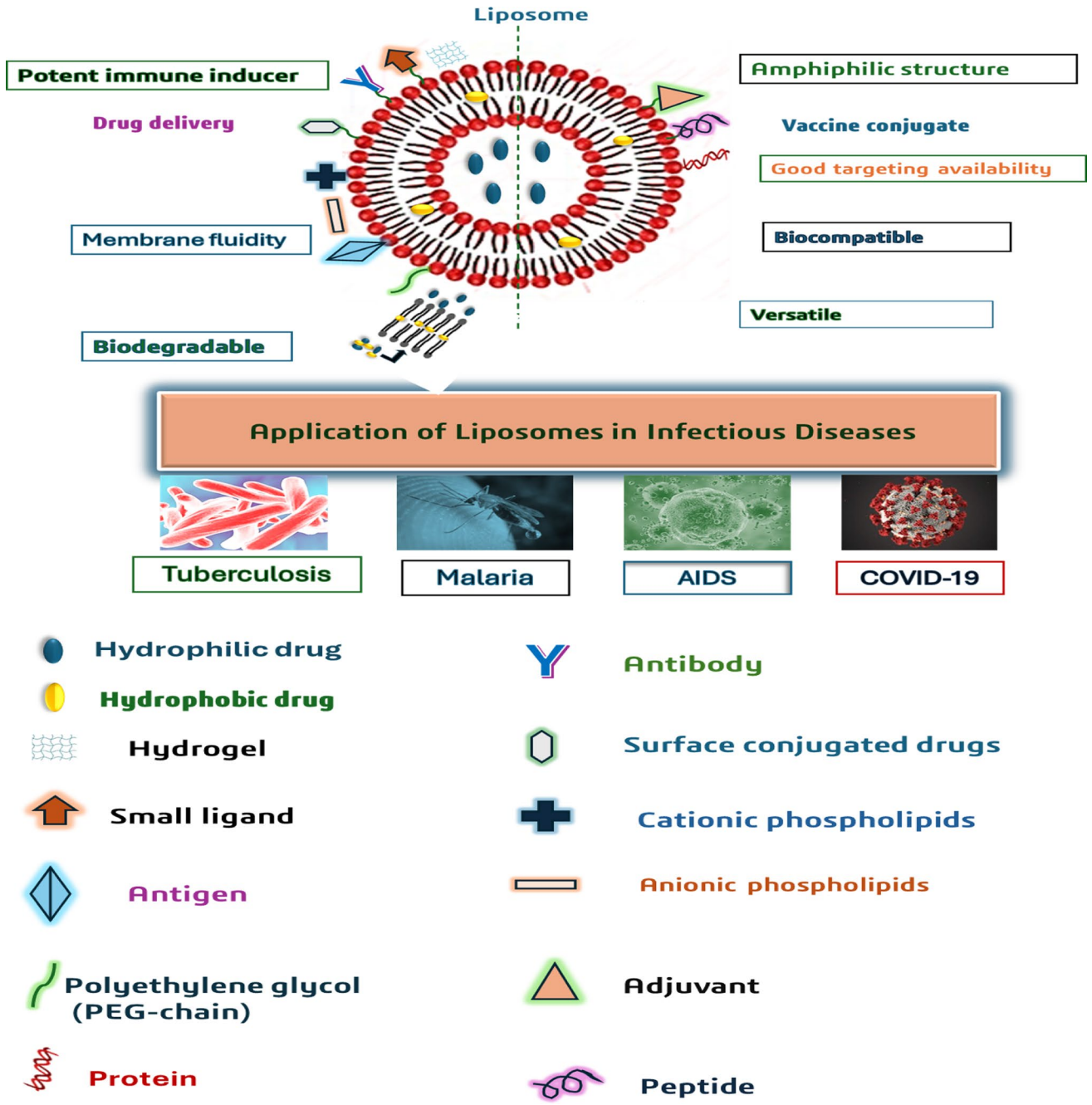


Fig. 1 Schematic of the functionalization of nanoliposomes and its applications in the treatment of infectious diseases adapted from [1]

Therefore investigating the design and application of NLs in the fight against infectious diseases has gained significant attention recently [12]. This review aims to provide a concise incursion into the latest approaches and novel (nano) liposomal strategies to treat and manage infectious diseases with several case studies to demonstrate their underlying applications in moving the science forward.

2 Limitations of conventional nanoliposomes in treating infectious diseases

Liposomes was first reported as an aqueous core surrounded by a lipid bilayer constituting either cholesterol, cationic, anionic, or neutral phospholipids. Given their flexible properties such as surface modification, size manipulation and different preparation methods, they have been widely explored to treat infectious diseases [13]. Clinical studies investigating their potential were initiated in the 1980s, demonstrated by the encapsulation of doxorubicin and amphotericin to obtain NLs with enhanced therapeutic efficacy [13–15]. Importantly, by optimizing the pharmacokinetics, biodistribution, functionalization (Fig. 2) and liposome size, relatively improved drug delivery to infected tissue has been achieved with reduced drug toxicity in vivo compared with free drug [13].

However, the limited effectiveness of conventional liposomes against pathogenic diseases remains a challenge due to several factors. For example, their limited capacity to target infectious microorganisms is a major limitation [16]. Although liposomes can entrap and deliver antimicrobials, their passive accumulation at infection sites is not sufficient to eradicate pathogens [7, 9]. Likewise, the duration of therapeutic effect is limited when conventional NLs are unable to provide sustained antimicrobial release at the site of infection [17]. Hence patient compliance and systemic toxicity arise due to the need for frequent administration or high doses to maintain therapeutic levels [18]. In addition, their susceptibility to biodegradation by the host immune system and the limited ability to penetrate microbial biofilms also limits their application to treat infectious diseases [19]. To improve the safety and therapeutic efficacy of liposomes, the highlighted constraints need to be overcome via the design of more efficient liposomes that can transport antimicrobials across pathogenic and biological barriers. Key strategies include optimizing their antimicrobial encapsulation efficiency, aligning particle size to pathogen morphology, extending the in vivo circulation time (half-life), targeted drug release and pharmaceutical stability [7, 20].

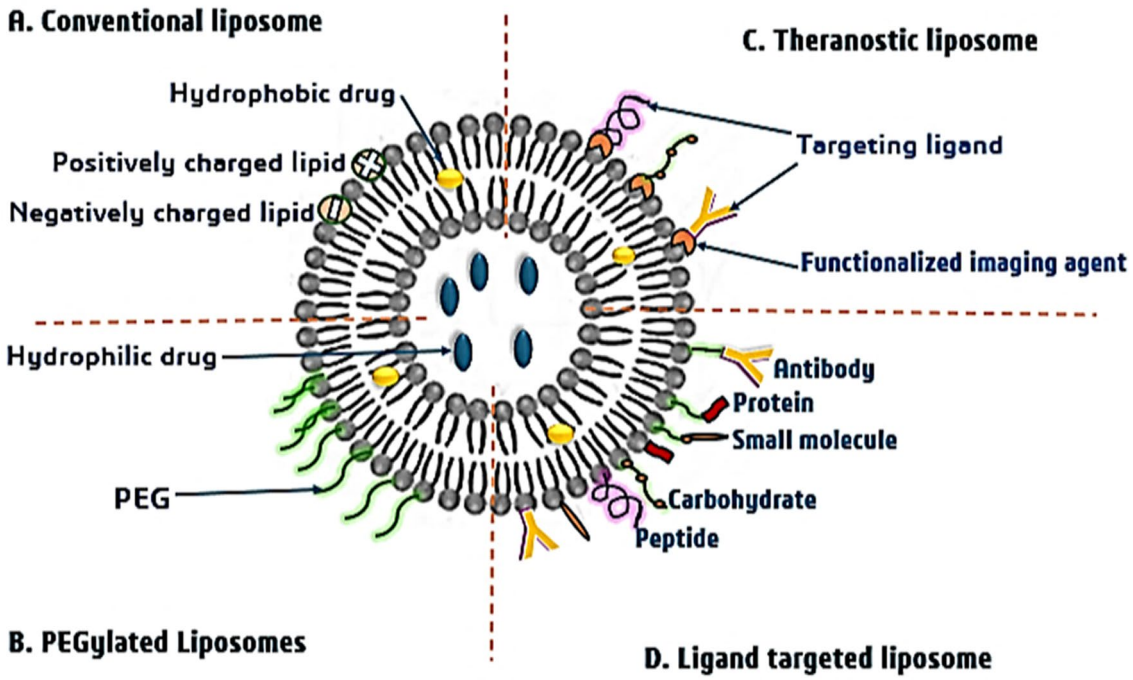


Fig. 2 Schematic of early liposomes showing the constituents and functionalization adapted from [13]

2.1 Inefficient antimicrobial encapsulation

Although conventional NLs may be suitable for antimicrobial delivery including hydrophobic and hydrophilic drugs, however, their low encapsulation efficiency remains a challenge for clinically meaningful application [21]. Inadequate antimicrobial drug loading and heterogenous drug distribution within the liposomal formulation is largely due to drug leakage during storage or within the systemic circulation [13, 22]. Antimicrobials may be poorly encapsulated due to the formulation method, resulting in drug-loading variation [23]. In addition, premature drug release due to drug-lipid bilayer interactions compromises drug entrapment and limits the control of drug delivery [24, 25]. These shortcomings accentuate the need for novel approaches to increase antimicrobial drug encapsulation efficiency and encourage homogeneous drug distribution within liposomal formulations [26].

2.2 Control of liposome particle size

Since conventional liposomes frequently have an array of particle sizes, data from particle population-based modelling is frequently heterogeneous with indistinct pharmacokinetic and biodistribution profiles [27]. The particle size distribution impacts the in vivo circulation time, tissue penetration, and cell uptake [28]. Furthermore, larger liposomes are difficult to effectively traverse biological barriers and penetrate target tissues [25]. Enhancing the pharmacokinetics of liposomes and improving their transport across physiological barriers are crucial for superior safety and therapeutic efficacy [29]. Advances in liposomal formulation attempt to circumvent this constraint by producing more uniform particle size distribution and eliminating size heterogeneity [29, 30]. These discoveries could broaden the range of liposomal applications by providing smart opportunities to align the liposome size to that of the target pathogens for precise and efficient antimicrobial chemotherapy for infectious diseases [1, 31].

2.3 Reduced in vivo longevity

The relatively short in vivo half-life or systemic circulation time of conventional NL is also a major limitation reducing the efficacy of antimicrobial chemotherapy, particularly for blood infections (sepsis) and other secluded tissue sites infected [13]. The short survival time is due to rapid clearance from the systemic circulation after administration due to enzymatic degradation reducing the therapeutic window at the site of action [32, 33]. This also leads to administering higher doses, resulting in harmful side-effects, premature drug release and decreased therapeutic efficacy due to systemic instability and the propensity to fuse with cell membranes [22, 24]. Restrictive biological barriers such as the blood–brain barrier and the stratum corneum of the skin also impedes the transport of conventional liposomes for certain infections [34]. Novel strategies that increase the pharmaceutical stability, evade immune clearance, and extend the in vivo circulation time can favorably increase the use of liposomes as a more efficient drug delivery strategy for infectious diseases [35].

2.4 Non-targeted (uncontrolled) release of antimicrobials

Indiscriminate release of antimicrobials from conventional liposomes is a major factor limiting its wider clinical application. Uncontrolled drug release leads to dose variation, therapeutic failure, side-effects and antimicrobial resistance [36, 37]. This includes premature drug leakage due to poor liposome intrinsic stability [38]. Enzymatic degradation, changes in pH or temperature, and an inclination to aggregate with cell membranes are also contributing to the poor control of liposomes to provide predictable drug release kinetics for infectious diseases [22, 33]. The physicochemical properties of the entrapped drug, the composition and membrane configuration of the liposome can also cause uncontrolled drug release kinetics. Drug-lipid interactions can lead to instability and leakage during liposome manufacturing and storage [13, 39]. The pattern of drug release is also altered by changes in liposome topical morphology, dimensions, and membrane integrity [30, 35, 40]. Therefore, novel approaches have been explored to address these challenges, such as the use of stimuli-responsive liposomes that are pH-, temperature-, and enzyme-responsive. Furthermore, the incorporation of ligands to provide targeted site-specific drug delivery has also been explored [41]. These contemporary approaches maximize the effectiveness of conventional liposomes by enhancing their accuracy and predictability of drug release. Several factors, such as the lack of the inherent targeting moieties on the surface of conventional liposomes, limits their ability to identify and bind to specific diseased cells or tissues, which is a major factor causing non-specific liposome targeting [38].

In the absence of targeting mechanisms, reduced therapeutic efficacy and off-target effects arise from the distribution of liposomes throughout the body without containment to the diseased site [22]. Their heterogeneity in vivo in the presence of endothelial cell barriers (ECB) and the reticuloendothelial system (RES), liposomes are sequestrated to non-targeted tissues or organ. The relatively larger size of conventional liposomes also limits site-specific accumulation and renders them vulnerable for clearance by the RES and leaky vasculature [42]. Therefore, the formulation of novel NLs with active targeting can delivery antimicrobials at pathological regions of interest to enhance treatment efficacy, capitalizing on the increased permeability and retention effect in tissues [43, 44].

2.5 Chemical and physical instability

The instability of conventional liposomes is caused by various chemical and physical factors. Frequent interactions between the liposomal membrane and the encapsulated drug leads to drug degradation or alteration. This also occurs with exposure to environmental factors such as changes in pH or in vivo enzymatic attack resulting in unpredictable therapeutic outcomes [33, 45]. Physical instability relates to changes in liposome size, shape, or structure over time. An array of variables can reduce the effectiveness of liposomal drug carriers and restrict their use clinically such as aggregation, fusion, or drug leakage due to bi-layer disruption [27, 46]. Poor efficiency in drug loading also limits the therapeutic efficacy [13, 33]. The propensity of conventional liposomes to fuse or aggregate with cell membranes influences their in vivo circulation and site-specific delivery to infected cells or tissues [35, 44]. Novel strategies to improve the physical and chemical stability of liposomes have been investigated using novel lipid compositions, stabilizing agents, and advanced manufacturing techniques [33, 47]. Hydrogels have been introduced with polymers to provide structural support and reduce the tendency for liposome fusion and aggregation [48–50].

3 Novel strategies to overcome the limitations of liposomes to treat infectious diseases

The potential to improve liposomal delivery systems via various functionalization strategies is huge in the domain of treating infectious diseases precisely with refined and targeted interventions [44, 51]. Functionalizing liposomes entails modifying their surface to incorporate particular targeting ligands, therapeutic elements or coatings to improve their capacity to interact with their intended targets [52]. Table 1 highlights some of the approaches used to modify or functionalize liposomes to precisely treat infectious diseases. Liposome functionalization provides an adaptable approach to improve antimicrobial targeting and therapeutic efficacy. In the context of infectious diseases such as TB, pneumonia, COVID-19, herpes, HIV, aspergillus, malaria, and leishmaniasis, liposomal functionalization (either stealth, bio-inspired/biomimetic or stimuli-sensitive) can improve antimicrobial delivery, provide immune modulation (HDT), and diagnostic capabilities [53, 54].

3.1 Stealth liposomes

Stealth (nano)liposomes is a strategy adopted to prevent the premature clearance of liposomes from the systemic circulation, prolong their circulation time and exploit the leaky endothelium effect [66]. They are designed with mixed lipid chains coated or stabilized with biomaterials such as polyethylene glycol (PEG) [67]. The stealth effect promotes accumulation at target sites, including infectious foci, leading to improved therapeutic efficacy [68]. They have unique characteristics including nanosize and structure thus suppressing drug extravasation and also maximizing the vascular permeability as drug accumulation in the tissues or cells increases [69, 70]. Since stealth NL circulates for an extended time, they can also provide sustained drug release and function as a reservoir for prolonged antimicrobial drug release. Therefore, antimicrobials can be exposed to the infection site for longer periods. Furthermore, the improved stability and minimized liposome clearance by the immune system, enhances drug bioavailability and penetration into microbial biofilms to address this challenge [17, 71]. PEGylation produces stealth NLs with a PEG chain modified surface [67]. They are known to prolong systemic circulation, enhance stability, and improve accumulation at the target site while minimizing recognition by the RES [50]. PEGylation enhances drug bioavailability from NLs by stabilizing liposomes and decreasing rapid elimination by the immune system. Targeted drug delivery can also be achieved with PEGylation by lowering the non-specific interactions and prolonging the residence time [72]. The incorporation of PEG chains on the liposome surface facilitates passive accumulation into target tissues by minimizing interaction with the RES [67]. The function of PEGylated liposomes depends on the physicochemical features of the liposomal membrane, its composition,

Table 1 Approaches used to functionalize nanoliposomes to treat infectious diseases

Liposome archetype	Lipid composition	Functionalization strategy	Infectious disease application	References
Cationic liposomes	DMPC, Cationic surfactants, DODAC, lecithin	Photosensitizer m-tetrahy-droxyphenyl-chlorin (m-THPC) incorporation	Methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* (*E. coli*)	[55]
Peptide-modified Azithromycin-loaded liposomes	Soybean lecithin, cholesterol	Attachment of the amphiphilic choles-teryl DP7-C peptide	Methicillin-resistant *Staphylococcus aureus* bacterial strain (MRSA)	[56]
Anti CD4 and dendrimeric peptide nano-liposome	Hydrogenated soy lecithin, DSPEm-PEG2000, Lipoid S100, DSPE-PEG2000-COOH, cholesterol	Anti-CD4 antibody/peptide dendrimer (PD2) attachment	Methicillin-resistant *Staphylococcus aureus* bacterial strain (MRSA), HIV	[57]
Anionic liposomes	DSPG, DPPG, DMPG, DSPC, DPPC, HSPC, MPEG2000-DSPE, DOTAP cholesterol	Protein corona inclusion	Methicillin-resistant *Staphylococcus aureus* bacterial strain (MRSA)	[58]
Azithromycin-propylene glycol liposomes	EPC, EPG, SPC-3, SLPC-80	Modification with Propylene glycol	Planktonic and biofilm-forming *Escherichia coli* strains and intracellular *Chlamydia trachomatis*	[59]
Invasin-surface functionalized liposome	DPPC, DPPE-GA, cholesterol	InvA497 incorporation	Enteropathogenic bacteria *Yersinia pseudotuberculosis/Salmonella enterica*	[60]
Inhalable Liposomal Amikacin	DPPC, cholesterol	Aerosolized	*Mycobacterium subsp. hominissuis* avium, *Mycobacterium abscessus* strains	[61]
Liposomes—hybrid nanoparticles	mPEG-PLGA, Lecithin, PEG-DSPE-Mal 2000	FITC grafted anti-mouse CD4, and APC anti-mouse CD8α antibody	Humoral and cellular immune responses	[62]
Tat-functionalized liposomes, fusogenic liposomes	DOPE, DPPC, CHS, DSPE-DSPE-PEG_{2000}-MAL, EPC	Tat peptide (Cys-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-NH_2), Tat47–57	*Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus,* methi-cillin susceptible aureus and *Escherichia coli*	[63]
Colistin bioinspired liposomes	DPPC, DPPE-GA, cholesterol	Extracellular adherence protein (Eap)	*Salmonella enterica*	[64]
Multifunctional targeted liposomes, targeted rifampicin and ofloxacin PEGylated liposomes	NHS-PEG2000-DSPE, DSPE-PEG2000, Soy PC, Cholesterol, DSPE-PEG_{2000}-Folate	Wheat germ agglutinin, FR+, TC, SPEC imaging agent incoporation	Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*, BCG *bovis* (Pasteur strain)	[65]

DMPC, 1,2-Dimyristoyl-*sn*-glycero-3-phosphatidylcholine; DSPG, (1,2-Distearoyl-sn–glycero-3-phosphoglycerol); DPPG, (1,2-Dipalmitoyl-sn–glycero-3-phosphoglycerol); DMPG, (1,2-Dimyristoyl-sn–glycero-3-phosphoglycerol); DSPC, (1,2-Distearoyl-sn–glycero-3-phosphocholine); DPPC, (1,2-Dipalmitoyl-sn–glycero-3-phosphocholine); HSPC, (Hydrogenated soybean phosphatidylcholine); DOTAP, (1,2-Dioleoyl-3-trimethylammonium-propane); EPC, Egg phosphatidylcholine; EPG, Egg phosphatidylglycerol; SPC-3, Hydrogenated soybean phosphatidyl-choline; SLPC-80, Monoacyl phosphatidylcholine; mPEG-PLGA, Poly[(ethylene glycol)-*co*-(D, L-lactide-*co*-glycolide)]; PEG-DSPE-Mal 2000, 1,2-Distearoyl-sn-glycero-3-phos-phoethanolamine-N-[maleimide(polyethyleneglycol)-2000]; DOPE, 1,2-Dioleoyl-*sn*-glycero-3-phosphatidylethanolamine; CHS, Cholesteryl hemisuccinate; DPPE-GA, 1,2-Dipalmi-toyl-sn-glycero-3-phospho-ethanolamine-N-(Glutaryl); NHS-PEG, N-hydroxysuccinimidyl-PEG2000-DSPE; DODAC, Dimethyldioctadecylammonium chloride

the nature of the entrapped drug and environmental triggers at the target site [72]. For example, inclusion of stimuli-responsive elements within the NL membrane structure can activate drug release in response to particular stimuli such as changes in pH or the presence of specific molecules at infected sites (Fig. 3) that facilitate sustained and targeted antimicrobial release [73, 74].

The interest in stealth liposomes has led to the development of PEGylated liposomes loaded with ofloxacin and rifampicin for theranostic application in the treatment of Mtb infection using hydrogenated phosphatidylcholine and DSPE-PEG2000-Folate lipids. Studies reported gradual drug release from PEGylated liposomes [75] with ofloxacin diffusion due to concentration gradients and lipidic membrane biodegradation, whereas rifampicin was released gradually due to slower partitioning from the lipid than the surrounding aqueous layer (a depot effect). In vivo scintigraphic investigations using a mouse model of TB infection revealed increased absorption at infected lesions. Minimal uptake was observed in the blocking imaging studies, confirming precise drug targeting.

Akshi Singla and colleagues [76], developed hetero-multivalent targeted liposomes functionalized with host cell glycans capable of increasing the delivery of ciprofloxacin antibiotic to the site of infection for the treatment of *Pseudomonas aeruginosa* Infections. In comparison with nontargeted liposomes, they demonstrated that greater numbers of targeted liposomes are found in the circulation, as well as at the site of *P. aeruginosa* (PAO1) infection in the thighs of CD-1 mice. They reported no discernible variation observed in the uptake of PEGylated, nontargeted, and targeted liposomes by J774.A1 macrophages. Mice infected with PAO1, and treated ciprofloxacin-loaded, hetero-multivalent targeted liposomes displayed a greater survival rate than mice given ciprofloxacin-loaded, nontargeted liposomes together with free ciprofloxacin. Thus, liposomes functionalized with host cell glycans target *P. aeruginosa* achieved increased retention of the liposomes in the circulation, accumulation at the site of infection, and increased survival time in a mouse surgical site infection model and are regarded as a potential strategy to improve the outcomes in patients infected with *P. aeruginosa*.

The efficacious loading of the antimalarial drug trans-platinum chloroquine diphosphate chloride (PtCO) into PEGylated neutral and cationic liposomes for resistant malaria parasites was also explored by Ibrahim and co-workers [77]. They reported PEGylated neutral and cationic liposomes that showed minimal PtCQ leakage after storage at 4 °C. In vitro culture conditions at 37 °C for 72 h also showed minimal drug release. These findings support the development of future in vivo (nano)liposomal delivery systems that target the malaria parasite.

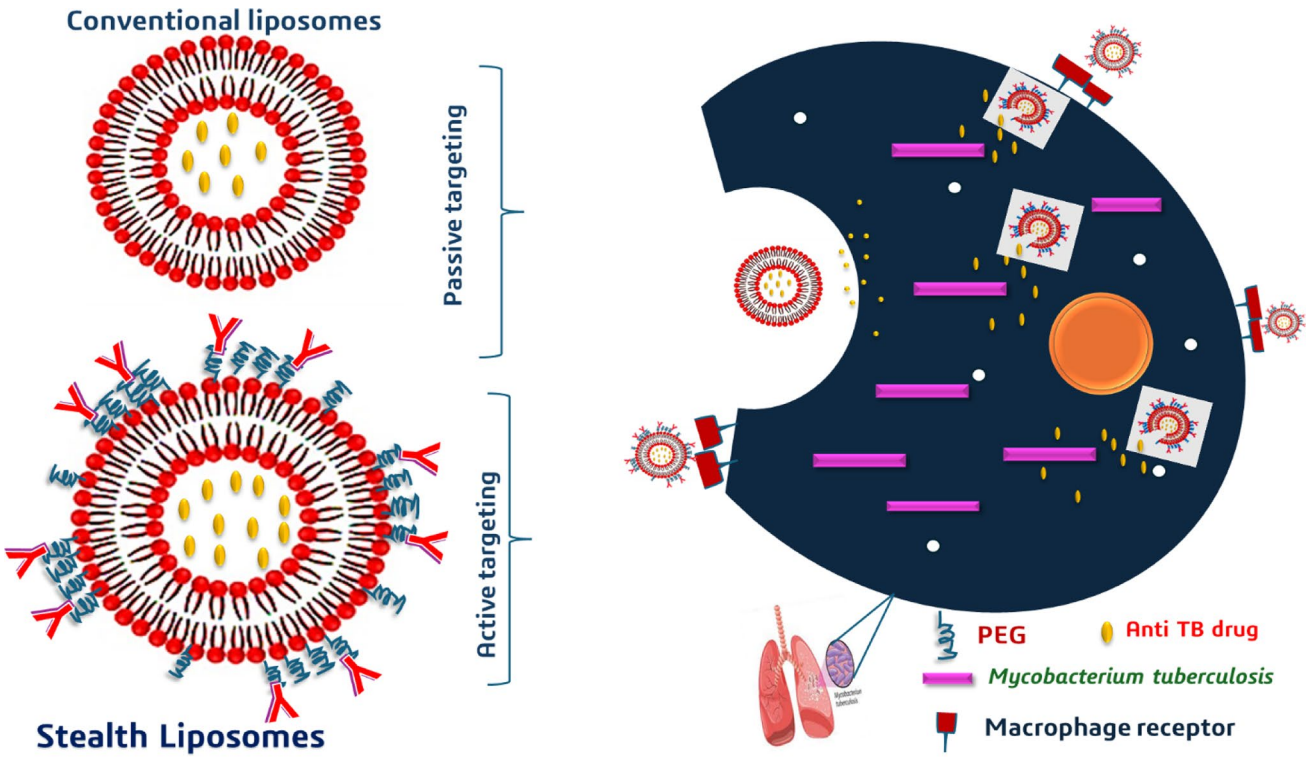


Fig. 3 Schematic illustration of PEGylated liposome coupled with functionalized ligand for targeted drug release in TB treatment adapted from [84]

3.2 Bioinspired and biomimetic (nano)liposomes

Investigation into bioinspired and biomimetic NLs has gained prominence recently as an innovative strategy to produce more precise liposomal therapeutic modalities to treat infectious diseases [78]. These NLs are modelled on naturally occurring biological systems with the aim to enhance targeting, drug distribution, and efficacy of antimicrobial agents by mimicking the structural and functional characteristics of infectious pathogens [79, 80]. This includes immuno-liposomes, fusogenic liposomes and stimuli-responsive liposomes (pH, light and thermal). The targeting properties of bioinspired/biomimetic NLs benefit from the design principles of nature [79]. These liposomes can specifically recognize and interact with infectious pathogens, allowing accurate localization and accumulation of antimicrobials at infection sites. Biomimetic components replicate the surface features of particular cell types or microbial structures [81]. In overcoming the limitations of conventional NLs, bioinspired liposomes can improve the safety and efficacy of antimicrobial chemotherapy. Through the integration of biomimetic elements, such as cell membrane-derived components or pathogen-mimicking structures, bioinspired liposomes use biological recognition systems to augment their interactions with infectious agents [82]. The ability to elude immune monitoring, cross microbial barriers, and exert targeted antimicrobial activity is made possible by biomimetism [35]. Biomimetic NLs can also be designed to incorporate bio-responsive and stimuli-sensitive materials, leading to more precise treatment strategies that adapt to the dynamic microenvironment of pathogens at infection sites [82, 83].

3.2.1 Immunoliposomes

Immunoliposomes are novel nano-liposomal drug delivery system coupled with surface ligands or antibodies for targeted antimicrobial delivery to specific cells or tissues [13, 51]. This targeted strategy can reduce off-target effects while increasing antimicrobial drug effectiveness. They are particularly promising to treat infectious diseases since they can enhance the immune response and propensity to absorb antimicrobials [84]. Immunoliposomes are designed to identify and attach to particular immune-modulating cells or tissues using ligands or antibodies (Fig. 4) which tiggers the release of the therapeutic agent to the active site [85, 86]. Different types of block-copolymers and lipids can be improved before functional groups are added. For example, in the commercially available formulation of a modified dibenzocyclooctyne

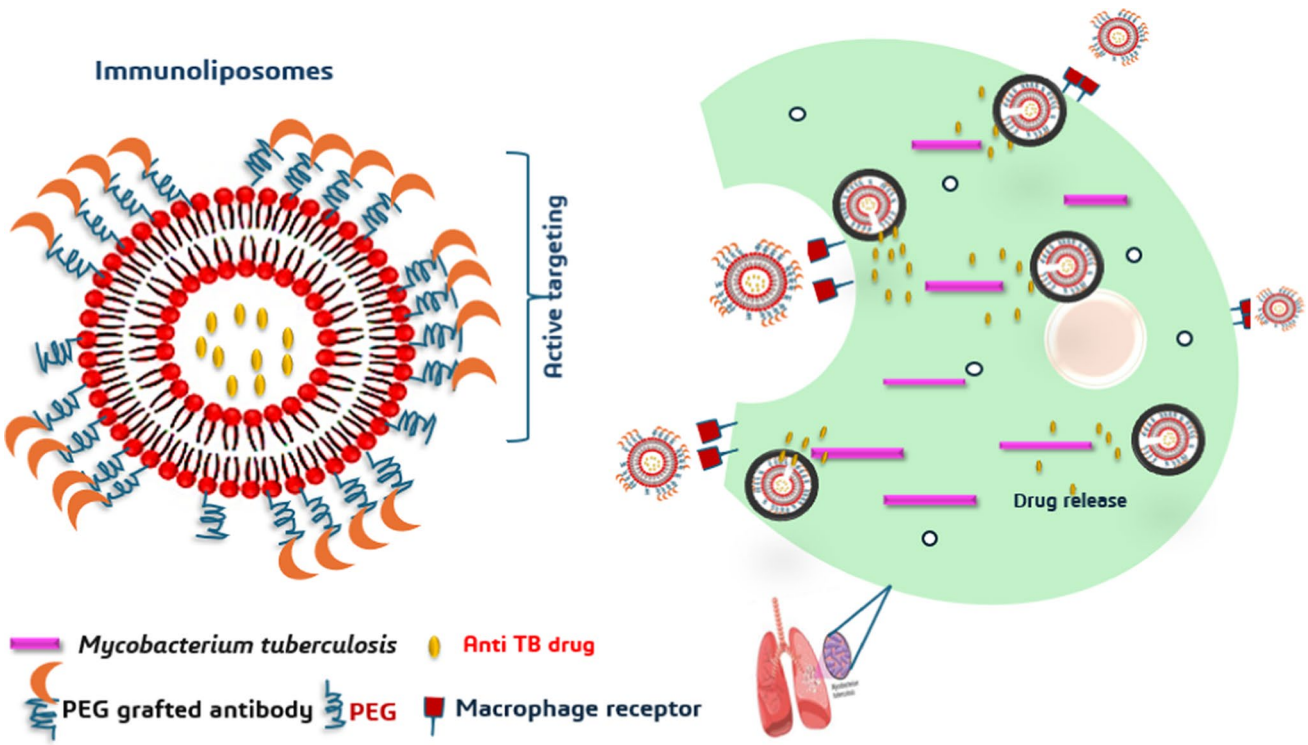


Fig. 4 Diagrammatic depiction of immunoliposome drug release mechanism in TB treatment adapted from [84]

(DBCO), a functional lipid (Immunosome®-DBCO) applied in liposome formulation, functional DBCO groups are added directly through the phospholipid before the liposomes self-assemble [87]. Immunoliposomes can also improve immune cell absorption and increase the efficacy of antimicrobial chemotherapy. Their flexibility allows for the encapsulation of hydrophilic and hydrophobic drugs as well as combination chemotherapy to target different aspects of infected cells, tissues, or organs [70]. Examples include toxin neutralization, host immune response regulation, and bacterial replication [70]. Immunoliposomes have also proven effective in immune stimulation and are regarded as a prolific approach to target dendritic cells and stimulate $CD8^+$ and $CD4^+$ T cells. Therefore, they have a significant advantage to advance the efficacy of antimicrobial chemotherapy [66, 88].

In recent studies by Nigam et al. [89], they showed a modified immune response in mice exposed to liposomal allergens of Aspergillus fumigatus. They successfully examined the immune modulating properties of anionic liposomes entrapped with glycoprotein antigens and allergens of *A. fumigatus*. They produced a liposome-entrapped glycoprotein antigens/allergens of *A. fumigatus* that provoked a Th1 type response in mice showing decreased peripheral eosinophilia. The analysis of lung tissue sections demonstrated a considerable decrease in eosinophil infiltration in mice that received the immunoliposome formulation. These findings showed that liposomal formulations of *A. fumigatus* allergens and/or antigens are promising as immunotherapy.

Coasta-Barborsa and the team developed lipid nano-delivery system containing recombinant *Candida albicans* chitinase 3 antigen as a potential vaccine against fungal infections [90]. They explored the adjuvant properties of the Dioctadecyldimethylammonium bromide and Monoolein containing *Candida albicans* Chitinase 3 for modulation of the immune response against fungal infections. They demonstrated the efficacy of the liposomes in delivering the antigen by the notable increase in cellular uptake observed upon encapsulating Cht3 in comparison to empty liposomes and safer for immunization procedure. The delivery of Cht3 liposomes subcutaneously induced a Th1/Th17 immune response profile, which was linked to the generation of elevated levels of antibodies directed against Cht3. Opsonizing mother-yeast at the cell scars, these antibodies identified both the native and recombinant forms of the protein, potentially upsetting cell separation and impeding yeast growth. Pursuant to their findings, the designed lipid antigen delivery system has the ability to enhance immune responses against fungal infections, which represents an appealing approach for the development of future fungal vaccines.

3.2.2 Tat-functionalized fusogenic liposomes

Tat-functionalized fusogenic liposomes are a particular form of liposomal carrier intended for precise drug delivery [44]. These liposomes have surface-mounted Tat peptide ligands that enable them to bind and detect specific cells or tissues [91]. The presence of Tat peptides facilitates the specific recognition and binding of the liposomes, enabling them to accumulate at the desired site of action [92]. Tat functionalized fusogenic NLs can fuse with the cell membrane (Fig. 5) of target cells due to fusogenic properties [93]. Through liposome fusion with the cell membrane, the Tat peptide improves cell internalization for effective intracellular antimicrobial delivery to target specific bacteria and viruses inside host cells. [94, 95]. This strategy prevents the release of drug within the endosomal milieu, a major challenge for conventional liposomes [96]. Tat functionalized fusogenic NLs thus represent an effective drug delivery pathway into the intracellular compartment to maximize the therapeutic efficacy [97]. The targeting characteristic is attributed to the Tat peptide surface functionalization that has the capacity to promote receptor mediated endocytosis by specifically targeting the cells that has shown a particular receptor [92]. Given the incorporation and attachment of the Tat peptide, it facilitates the intracellular delivery of therapeutic agents by promoting cellular uptake and endosomal escape [98]. Thus, the encapsulated drugs can be released from the Tat functionalized NLs once within the cells, guaranteeing that the intracellular pathogens will be directly affected, thus minimizing the potential for unwarranted effects and decreasing the exposure of the healthy cells to therapeutic compounds [68, 99]. With the implementation of this capability, infections or intracellular pathogens can be directly targeted, an area that may be difficult for conventional drug delivery approach to penetrate [100]. This approach, owing to the integration of Tat peptide, is capable of enhancing the potential of immunoliposomes by providing an exhaustive approach for targeted drug delivery [100].

A study on the encapsulation of vancomycin's spectrum of action against Gram-negative bacteria was reported by Nicolosi et al. [101] who designed a Vancomycin Tat-functionalised liposomes. The in vitro microbiological investigations revealed that the development of standard and wild strains of Gram-negative bacteria was suppressed to varying degrees. Conversely, against the same bacteria, neither the free antibiotic nor vancomycin-loaded conventional liposomes demonstrated any efficacy. They reported a minimum inhibitory concentration as low as 6 mg/L for vancomycin fusogenic liposomes against clinical isolates of *Escherichia coli* and Acinetobacter baumannii. Studies using scanning and

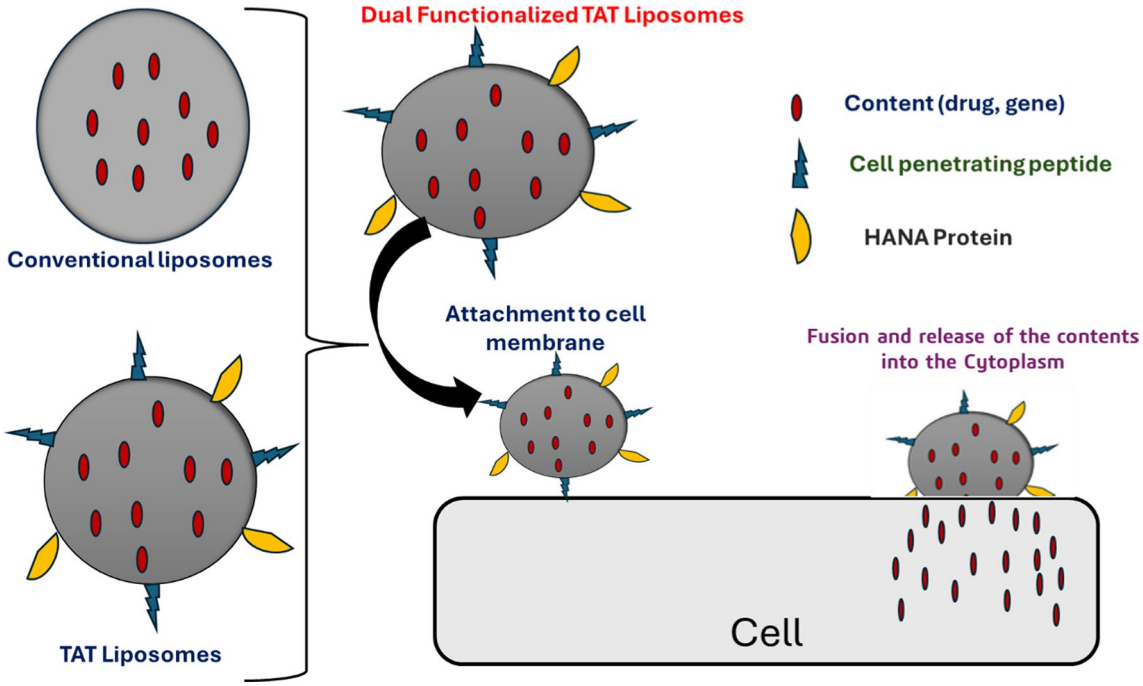


Fig. 5 Demonstration and application of the dual Tat peptide functionalized fusogenic properties of liposomes into the cytoplasm as adapted from [100]

transmission electron microscopy provided evidence that the nanovesicles can fuse with the outer membrane of *E. coli* and preliminary investigations suggested that this strategy may be a viable means of expanding the activity spectrum of vancomycin.

Scriboni and co studied the in vitro antibacterial activity of various liposomal formulations of large unilamellar conventional, fusogenic, and cationic vesicles against *S. aureus* biofilms through the encapsulation of the dual vancomycin. *S. aureus* strains ATCC 29213 and ATCC 43,300 (resistant to and susceptible to methicillin) [102]. They assessed the MIC on the formation and survival of biofilms and reported variations in the MIC of the drug-loaded liposomal formulations and the free vancomycin with respect to the two strains. There was no appreciable difference in the extent of biofilm growth suppressed. On the contrary, encapsulated fusogenic vancomycin unilamellar liposomes enhanced the antibacterial efficiency compared with other liposomal formulations and free vancomyscin, indicating a superior ability to permeate the biofilm, when treating mature biofilm.

3.2.3 Stimuli-responsive liposomes

Stimuli-responsive liposomes have emerged as a viable approach to selectively deliver and release antimicrobial drugs. Triggered release in liposomal carrier systems typically destabilizes membranes through local defects in bilayer membranes. This destabilization leads to the release of encapsulated drugs [103]. Different activation methods (Fig. 6) have been employed to respond to stimuli for drug delivery and include internal stimuli such as variations in pH, reducing agents, enzymes, and exterior stimuli such as light, magnetic fields, temperature, or ultrasound. These modifications facilitate site-specific drug release in the presence of particular stimuli (Table 2) [104].

3.2.3.1 pH-stimulated liposomes pH-stimulated liposomes (Fig. 7) are NLs that can enhance the bioavailability of antimicrobials at the desired site while remaining stable systemically until the site of infection is reached [104]. pH-sensitive liposomes are specifically engineered to detect and adapt to the varying pH levels found in target sites, which may differ from the typical pH of 7.4 in healthy tissues. This design enables the liposomes to enhance their effectiveness in these conditions [103]. pH is the primary and extensively utilized internal stimulus in pathological locations. NLs are said to be pH-sensitive if they can quickly change their shapes or properties in response to even small changes in pH in acidic or alkaline environments [108]. Acid-sensitive liposomes remain stable when exposed to normal physiological conditions with a pH of 7.4. However, they release drugs when exposed to acidic conditions with a pH of 5.0. This drug

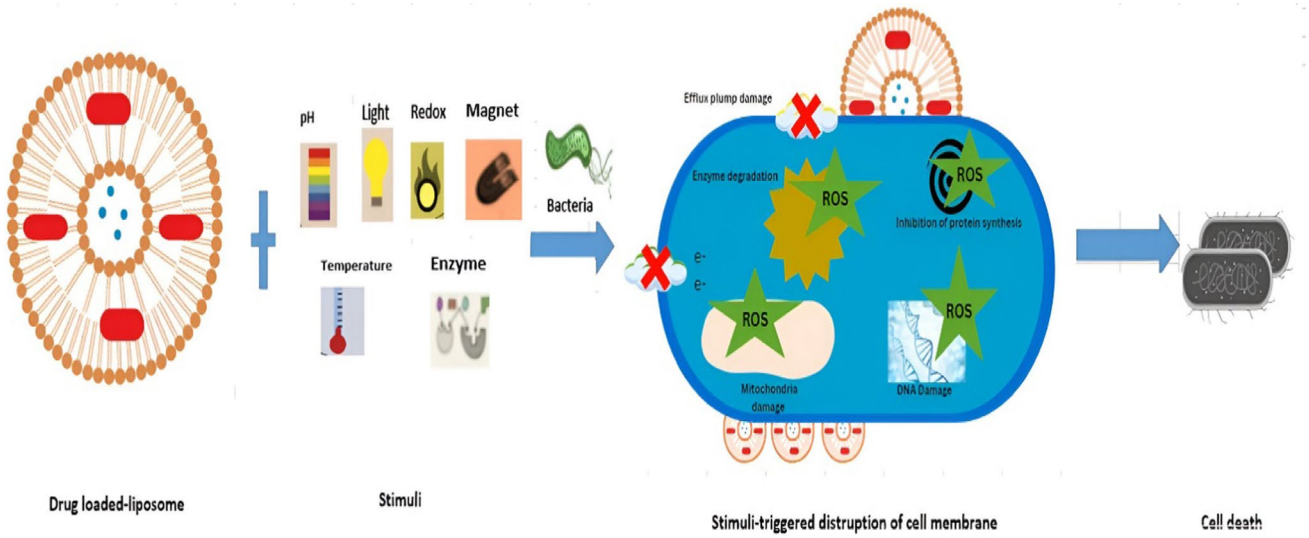


Fig. 6 Diagrammatic representations of drug loaded-stimuli sensitive liposomes showing the internal, external stimuli, and its antibacterial action adapted from [105]

release can occur through lysosomal endocytosis (Fig. 8) or due to the instability or fluidity of the liposomes' bilayer membrane in this acidic microenvironment. Liposomes sensitive to pH become unstable very quickly in acidic sites like endosomes. When the pH drops, the amphiphiles in the liposomes lose their acidic groups and become protonated, making them less stable [103]. pH-sensitive liposomes consist of the cone-shaped lipid dioleoylphosphatidylethanolamine (DOPE) and amphiphile cholesteryl hemisuccinate (CHEMS), which are neutral and slightly acidic respectively. The fusogenic activity these highly responsive liposomes exhibit can be attributed to DOPE within their lipid bilayer. When DOPE is dispersed in water, it creates a hexagonal structure instead of a bilayer structure. Additionally, pH sensitivity can be enhanced by utilising alternative lipids, such as dioleoylphosphatidylcholine (DOPC) or N-succinyl-DOPE. The lipids in question exhibit negatively charged moieties that can be effectively neutralized through acidification within the endosome, resulting in destabilization, merging with the endosomal membrane, and liberation of their contents. To produce pH-sensitive liposomes that are stable in biological fluids and capable of facilitating cellular internalization, fusogenic activity, and pH responsiveness, pH-sensitive lipids and amphiphilic stabilisers must be meticulously chosen. The widespread use of pH-sensitive liposomes is hindered by phagocytes' recognition of these liposomes in the RES. As a consequence, these carriers have extremely brief circulation half-lives. Grafting liposomal membranes with pegylated phospholipids is a viable strategy to elongate their circulation in the body and prevent their absorption by the RES [103, 109].

Garcia [110] successfully developed pH-sensitive liposomes with a Tat-functionalized structure for site-specific treatment of bacterial meningitis. Antibiotics are part of the usual treatment for meningitis. However, they are frequently ineffective due to the limited permeability of the BBB. The authors produced a pH-responsive (fusogenic) liposomal system functionalized with the TAT47-57 (TAT) peptide to treat bacterial meningitis. The TAT-functionalized liposomes loaded with vancomycin were made of phospholipid with molar ratios of DOPE: DPPC (Dipalmitoylphosphatidylcholine): CHS (Cholesteryl hemisuccinate): PEG-TAT at 40%, 15%, 35%, and 10%, respectively. The TAT peptide was linked to DSPE-PEG, resulting in PEG-TAT on the surface of the liposome. At 24 h, astrocytes (A) and endothelial cells (B) displayed cell viability after treatment with vancomycin, TAT-van-Lipo, TAT-lipo, and TAT alone ($p > 0.05$ against free antibiotic at 1 µg/mL, 2 µg/mL, and 5 µg/mL). The liposomes were also examined for their BBB permeability and antibacterial properties. The study hypothesized that fusogenic liposomes interacted with phospholipids in the bacterial outer membrane. As a result, the encapsulated vancomycin could enter the periplasm. The formulation exhibited the highest release rate at around pH 5, which reduced as the pH increased to 7. To study the interaction between liposomes and the BBB, liposomes tagged with a fluorescent marker were cultivated with brain endothelial cells and astrocytes. The liposomes and cells were then observed using an inverted microscope. Without bacteria, the liposomes did not contact the cells that line the BBB. In the presence of microorganisms, the medicated liposomes demonstrated a bactericidal action against methicillin-resistant *S. aureus*. The research indicates that using pH-activated functionalized liposomes can enhance the antibiotics' capacity to traverse the outer membrane of Gram-negative microorganisms [110]. In their study, Portilla et al. [111] effectively

Table 2 Summary of the modified stimuli-sensitive liposomes for the treatment of infectious diseases

Liposome archetype	Lipid composition	Active agent	Modification strategy	Infectious disease application	References
pH-sensitive liposomes	DOPE: DPPC: CHS	Vancomycin	TAT47-57 (TAT) peptide conjugation	Gram-negative microorganisms	[110]
pH-sensitive liposomes	NM	Antistaphylococcal endolysin LysRODI	None	*Staphylococcus aureus*	[111]
pH-sensitive liposomes	DOPE and CHEMS	Isoniazid	Zinc (II) phthalocyanine (PC) (hydrophobic photosensitizer) and hydrazone bonding (pH-labile linkage)	*Mycobacterium tuberculosis*	[113]
pH-sensitive liposomes	Soybean lecithin	Isoniazid	4-Hydroxy-benzaldehyde via a hydrazone bond to yield isonicotinic acid (4-hydroxy-benzylidene)-hydrazide (INH-HB)	*Mycobacterium tuberculosis*	[114]
pH-sensitive liposomes	NM	Isoniazid and Ciprofloxacin HCl	4-aminophenyl-α-D mannopyranoside (Man) as surface functionalized ligand	*Mycobacterium tuberculosis*	[115]
Light-sensitive liposomes	EPC	Carboxyfluorescein	Aluminium phthalocyanine disulfonic acid (AlPcS2)-photosensitizer	None	[118]]
Light-sensitive liposomes	DSPC, DOPC, MPEG-2000-DSPE or PEG-lipid)	Ciprofloxacin	Porphyrin-phospholipid (PoP)	*Bacillus subtilis*	[122]
Light-sensitive liposomes	DSPC and DSPE-mPEG2k	Antimicrobial peptides (AMPs), IRIKIRIK-$CONH_2$ (IK8)	poly(ethylene glycol) (PEG)-based gel (hydrogel) containing AMP-loaded liposomes, IK8-liposomes and lipid-coated nanorods- Au nanorods (AuNRs)	Gram-negative *Pseudonomas aeruginosa* and Gram-positive *Staphylococcus aureus*	[123]
Thermal-sensitive liposomes	Thermal-sensitive DPPC bilayers	Vancomycin	Black phosphorus quantum dots (BPQDs)-photothermal and pharmacotherapy	Methicillin-resistant *Staphylococcus aureus* (MRSA)	[121]
Thermal-sensitive liposomes	DSPC and quaternized cholesterol	Tobramycin	Cypate (cyanine dye), photothermal co-therapy	*Pseudomonas aeruginosa* biofilm	[127]

NM Not mentioned

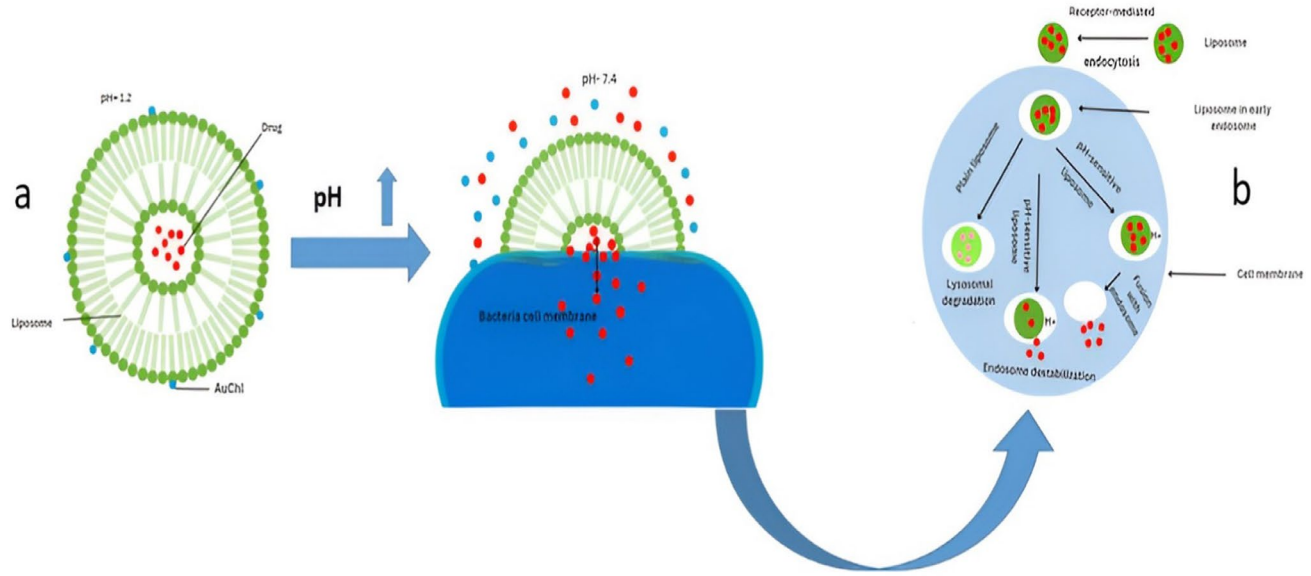


Fig. 7 A diagrammatic depiction of **a** pH-sensitive liposome for gastric antimicrobial delivery and **b** the lysosomal endocytosis of this pH-sensitive liposome [106, 107]

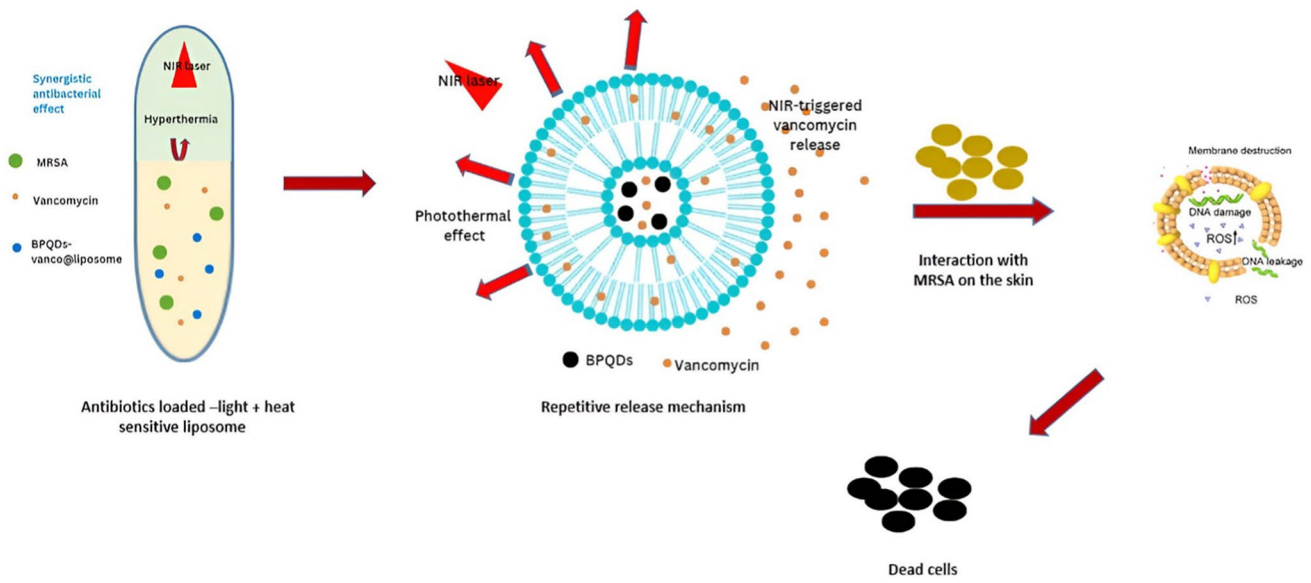


Fig. 8 A diagrammatic representation of BPQDs-Vancomycin-loaded light-sensitive liposome for local treatment of bacterial skin infection [121]

enclosed the antistaphylococcal endolysin LysRODI in pH-sensitive liposomes, resulting in an effective treatment against multi-drug-resistant bacteria. This study showed that the protein was enclosed within pH-sensitive liposomes with an efficacy of around 47%, maintaining its activity upon release from the nanocarrier. In addition, the enclosed endolysin achieved a remarkable feat, significantly decreasing the number of *S. aureus* cells by more than two logarithmic units in both liquid cultures and biofilms when incubated at pH 5. This impressive result underscores the effectiveness of LysRODI in combating drug-resistant bacteria [111].

TB is the primary cause of death attributable to infectious diseases. Liposomal encapsulation has been used to achieve controlled delivery of anti-TB drugs due to two main factors: (1) the need for protracted TB treatment and (2) the occurrence of frequent side-effects resulting from the low bioavailability of anti-TB drugs. Liposomes have been investigated to delivery anti-TB drugs because they are rapidly absorbed by alveolar macrophages, commonly

inhabited by the *mycobacterium*. The need to release drug dependent on space and time arises due to the considerable challenge of leakage in conventional liposomes for hydrophilic compounds like isoniazid (INH). pH-sensitive liposomes can specifically target macrophages, important for delivering drugs to specific sites affected by anti-TB. This targeting is possible because of the difference in pH between the biological fluids and the endocytotic compartments in the phagocytotic pathway, which are pH 7.4 and 4.5–6.5 respectively [112, 113]. Several pH-labile linkers, such as acetal, dimethyl maleate, ketal, oxime, imine, and hydrazone, have been explored for pH-dependent delivery [113].

Nkanga and Krause [113] developed a liposomal formulation controlled by pH for isoniazid (INH) connected to zinc (II) phthalocyanine (PC) by a hydrazine linkage. Throughout a 12-h examination into the release of drugs, pH-responsive liposomes released 22%, 41%, 97%, and 100% of INH into mediums with pH levels of 7.4, 6.4, 5.4, and 4.4, respectively. The rate at which INH was released from PC-INH-enclosed liposomes (PILs) was substantially higher in acidic states compared with a neutral environment. The formulation utilised had pH-dependent drug release for site-specific delivery. Using pH-labile linkages to connect hydrophilic active agents to hydrophobic molecules like phthalocyanines has the potential for controlled drug release [113].

In a study by Nkanga et al. [114], liposomes were created to enable the controlled release of isoniazid coupled with 4-hydroxybenzaldehyde, which depends on pH levels. This study also utilised hydrazone bonds as pH-activated links to regulate the discharge of INH from liposomes loaded with isonicotinic acid (4-hydroxy-benzylidene)-hydrazide (INH-HB). The INH-HB-loaded liposomes (IHL) exhibited varying release percentages over 12 h in different dissolution media with varying pH levels. This pH-dependent releasing behaviour is valuable in minimising INH loss caused by liposome leakage.

Bhardwaj et al. [115] have made a significant stride in the field by effectively delivering ligand-anchored pH-sensitive liposomes (TPSL) via a dry powder inhaler to the targeted cells of the lungs. The modified pH-sensitive liposomal system, loaded with isoniazid (INH) and Ciprofloxacin HCl (CIP HCl), and utilizing 4-aminophenyl-α-D-mannopyranoside (Man) as a surface-functionalized ligand, has shown promising results. The drug release investigations of the liposomes over 24 h demonstrated a gradual release at an alkaline pH (58–64%) in contrast to the macrophage pH (81–87%)—an acidic pH—where the release significantly accelerated due to the instability of pH-sensitive liposomes. The in vitro cellular absorption investigation showed a substantially higher concentration in alveolar macrophages employing ligand-anchored liposomes than unconjugated PSL. The in vivo investigation demonstrated that the highest drug accumulation in the lung was achieved by administering ligand-anchored PSL, in contrast to conventional PSL. This research has the potential to significantly impact the future of targeted medication therapy in pulmonary tuberculosis, underscoring the importance and relevance of the study.

3.2.3.2 Light sensitive liposomes The targeted delivery of compounds contained within liposomal system can be physically activated through light. To effectively employ light as a stimulus, photons must traverse biological tissues without causing any damage, triggering the release mechanism. Due to its low scattering and absorption coefficients, light can deeply penetrate biological tissues with wavelengths ranging from 600 to 900 nm. This unique characteristic ensures that living cells are minimally affected and minimal damage [103, 104]. Nevertheless, most light-sensitive components utilized in liposomes are triggered through UV or visible light exposure, which restricts their usage to areas near the body's surface [116]. One of the benefits of using light as a trigger is its versatility in adjusting several parameters including contact duration, wavelength, beam diameter, and laser strength to cater to different applications [117]. Light-sensitive liposomes can be formed by inserting photoactive molecules or photosensitizers (PS) (Fig. 8) into the liposomes' lipid membrane. This incorporation enables the release of trapped molecules upon exposure to light irradiation. PS can be incorporated into the hydrophilic interior of liposomes or the lipophilic interstitial space between lipid bilayers. Some examples of PS are benzoporphyrin derivative monoacid (BPD), chlorin e6 trimethyl ester (Ce6), aluminium phthalocyanine disulfonic acid (AlPcS2), and 5,10-di-(4-hydroxyphenyl)-15,20-diphenyl-21,23H-porphyrine (5,10-DiOH) [118, 119]. The photosensitizer in the bilayer of liposome generates reactive oxygen species (ROS), including singlet oxygen, upon exposure to light of a particular wavelength. This leads to chain breaks, lipid disintegration within the liposome`s membrane, and the discharge of entrapped payloads into the cytoplasm [120]. Thus, liposomes may deliver encapsulated medications spatially and temporally regulated, provided that an appropriate method for controlling lipid bilayer permeability is developed [118]. Utilizing a light stimulus for medication release facilitates a significant degree of control due to the external adjustability of variables, including photon intensity, concentration of PS, and absorption spectrum [119].

Randles and Bergethon [118] observed that the presence of PS aluminium phthalocyanine disulfonic acid (AlPcS2) changed the colloidal characteristics of the liposomal system. The adsorption of AlPcS2 onto liposomes enhanced the

rigidity of lipid bilayers and decreases permeability. The spectroscopic findings indicated that AlPcS2 formed an interaction with the phospholipid, increasing the stability of the lipid bilayer. The photosensitizer AlPcS2 resulted in a five-fold decrease in liposome permeability compared to when the photosensitizer was absent. This resulted in liposome systems that exhibit enhanced stability and could accommodate more significant quantities of the encapsulated substance for extended durations. Subsequently, upon exposure of the AlPcS2-liposome system to red light that might penetrate tissues, the lipid bilayer's permeability rose by a factor of ten compared to the initial level. The release mechanism of AlPcS2 was shown to be mediated by singlet oxygen through type II photodynamic action. Randles and Bergethon's research [118] established that this behaviour signifies a distinctive photo-release mechanism for liposome-mediated drug administration. Therefore, exposing the target tissue to light initiated the discharge of cargo, allowing medications to be released locally. Furthermore, light-activated liposome released intracellular improved cargo delivery to the cytoplasm. During endocytosis, most liposomes became ensnared and eventually degraded within lysosomes. Given that the cargo has deteriorated due to liposome degradation, it was critical to assist the release from the endolysosomal pathway. As a result, the capability to liberate medications in regulated modus improves localized concentrations and bioavailability, which potentially increased therapeutic benefits [119].

The excessive or incorrect use of antibiotics and the presence of their remnants in the environment contribute to the rise and pervasiveness of drug-resistant microorganisms, which in turn causes significant health complications. If the precise control of drug dosage over an extended period at a specific site can be achieved, using light-activated liposomes will become widespread in antimicrobial chemotherapy. Light-activated liposomes that allow for many repeating medication releases have significant potential in antibacterial therapy. Repeatability is crucial since it ensures stability and precise control over the dosage, preventing excessive usage of antimicrobials. By adjusting laser parameters, such as duration and power, one can accurately monitor and estimate the precise amount of dosage delivered. Repeatability can prevent issues with antibiotic-resistant bacteria and effectively treat infections. Furthermore, the functionality of light-activated liposomes offers the convenience of preserving the medication for extended periods of use. With a single application, the dose can be controlled later through laser irradiation, eliminating the need for additional doses. In essence, repeated light-stimulated liposomes present three distinct merits over traditional liposomes: 1. Extended duration of administration, 2. Combination therapy with controlled dosage, and 3. Enhanced therapeutic impact with the combined use of chemotherapy, photodynamic therapy, and photothermal therapy [117]. This efficient and precise control over dosage enhances the therapeutic impact and instils confidence in the potential of light-activated liposomes in antimicrobial treatments.

In their study, Ghosh et al. [122] developed light-activated liposomes using porphyrin-phospholipid (PoP) that contained ciprofloxacin. These liposomes were engineered to release the medicine rapidly when exposed to light. Over 90% of the antibiotic was released from the liposomes in less than 30 s when exposed to 665 nm (red light) irradiation. The ciprofloxacin-loaded PoP liposomes effectively suppressed the development of *Bacillus subtilis* in liquid media by being taken up by the bacteria. Importantly, the study demonstrated the potential for remotely encapsulating antibiotics into photo-triggered liposomes, a finding that could lead to significant advancements in localised antibiotic therapy.

Antimicrobial peptides (AMPs) present a promising alternative to antibiotics, as they physically damage bacterial membranes, leading to fast bactericidal effects. However, their practical application has been impeded by vulnerability to protease degradation [123]. Moorcroft et al. [123] effectively addressed bacterial multidrug resistance to AMPs using the co-loading of liposomes containing the model AMP, IRIKIRIK-CONH2 (IK8), and gold nanorods (AuNRs) within a poly(ethylene glycol) (PEG) hydrogel. The authors demonstrated the capability to safeguard encapsulated substances from proteolysis and presented the inaugural occurrence of triggered AMP release. Laser irradiation at 860 nm, at 2.1 W cm^{-2} for 10 min, induced the photothermal release of IK8, demonstrating bactericidal efficacy against Gram-negative Pseudomonas aeruginosa and Gram-positive *S. aureus*. Moreover, elevating the laser intensity to 2.4 W cm^{-2} resulted in the thermal augmentation of AMP activity. The photothermal-triggered release and augmentation of AMP potency were demonstrated to eradicate two instances of fresh *S. aureus*, showing that the therapeutic gel had the potential for numerous treatment cycles. This successful demonstration of the hydrogel system's capabilities reassures us of its potential for treating pathogenic microorganisms.

3.2.3.3 Thermal sensitive liposomes Temperature-responsive or thermo-responsive liposomes (TRLs) (Fig. 9) are very efficient nanocarriers for targeted drug delivery applications. This is because conventional liposomes have previously been granted clinical authorization for use. Site-specific administration minimizes drug contact with normal tissue and enhances the medicine's therapeutic effectiveness while minimizing side effects [104, 124]. One of the main variables significantly affecting cell metabolic activities is temperature. For intracellular chemical reactions, the usual body tem-

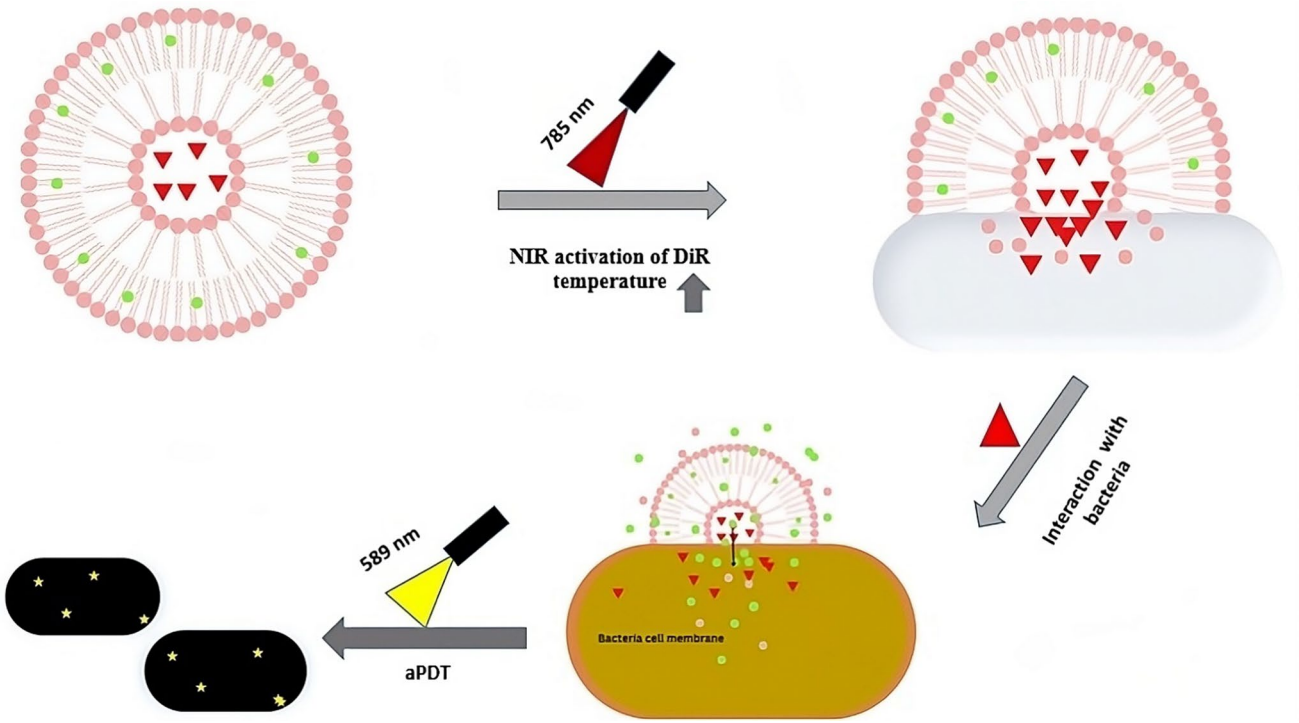


Fig. 9 A depiction of temperature sensitive liposome drug release mechanism for efficient antimicrobial therapy [126]

perature of mammals is 37 °C. TRLs are specifically engineered to facilitate the release of drugs in locations with elevated temperatures (T > 39 °C), such as diseased areas, when the temperature is higher than the normal physiological level. The use of moderate hyperthermia (HT), which involves raising the body temperature slightly above average, has been widely employed in conjunction with radiotherapy and chemotherapy to enhance the effectiveness of these therapies while minimizing adverse effects [104, 116].

TRLs can release pharmaceuticals that are enclosed within them when the temperature of the lipid bilayer reaches its melting phase transition temperature. By gently heating tissue to a temperature of 41–42 °C, the medication can be delivered locally within the heated lesion, as demonstrated by Mallick and Choi in 2014. Conventional thermosensitive liposomes consist of lipids (dipalmitoylphosphatidylcholine (DPPC), distearoyl phosphocholine (DSPC), and hydrogenated soy phosphocholine (HSPC)) that change from a solid to a liquid state at temperatures slightly over the typical body temperature. The regulated liberation of drugs can be improved by applying mild HT. HT can enhance the therapeutic efficacy of targeted drug release of TRL by promoting blood flow to the affected area and improving the ability of target cells to absorb the released medications [125]. Thermosensitive liposomes can also be created using hydrophilic lysolipids, specifically mono palmitoyl-phosphatidylcholine (MPPC), with a transition temperature (Tm) ranging from 39 to 42 °C. These liposomes are formed by incorporating MPPC into DPPC bilayers. Studies conducted by Ta and Porter [125], and Mallick and Choi [124] have demonstrated the employment of such liposomes. Lysolipids-TRL decreased the phase transition temperature of conventional thermo-responsive preparations from 43 to 39–40 °C. This led to a rapid and substantial rise in the payload released when heated. As a consequence, the amount of drug released upon heating swiftly and substantially rose (about 50% within 20 s of heating at 42 °C) [125]. An alternative approach to enhance the temperature sensitivity of liposomes involves using synthetic polymers that induce membrane disruption upon heating. These particular polymers can enhance the temperature-responsiveness of preparations unaffected by temperature or improve the temperature-responsiveness of liposomes that are already sensitive to temperature by accurately regulating the ratio of lipids and polymers. Temperature-responsive polymers includes; poly(N-isopropylacrylamide) (p(NIPAAm)), poly(ethylene glycols) (PEG), and peptides [124, 125].

In their study, Zhang et al. [121] developed antibacterial liposomes activated by photons. These liposomes are aimed at treating skin infections by combining photothermal and pharmacotherapy. The liposomes comprised thermal-sensitive DPPC bilayers and contained black phosphorus quantum dots (BPQDs) and vancomycin, a pharmaceutical. This research aims to create a photon-regulated anti-bacterial system capable of efficiently eradicating drug-resistant microorganisms

and prevent the development of new microorganism resistance. The created antibacterial platform effectively released vancomycin in a regulated way in terms of site, time, and dosage. This was achieved by including co-encapsulated BPQDs, which can generate heat when stimulated by near-infrared light. The generated heat disrupts the thermal-responsive liposomes, enabling the controlled release of vancomycin. The local rise in temperature generated by the photothermal impact of BPQDs can also result to the efficient eradication of microbes, even drug-resistant pathogens. In addition, the researchers of this study discovered that the hybrid light-thermal sensitive liposomes can reduce the required dosage of antibiotics. This is beneficial as it aids in preventing antibiotic misuse and developing antibiotic-resistant bacteria, commonly known as superbugs. The developed antibacterial platform, which combines photothermal and pharmacotherapy, has shown remarkable antibacterial efficacy in vivo for treating a cutaneous abscess produced by bacteria resistant to drug. The created light-controlled antibacterial platform has potential applications in anti-infective therapy and precision medicine, as it can effectively kill antibiotic-resistant bacteria and prevent bacterial resistance [121].

Biofilm, a complex entity intricately linked to persistent diseases, presents a significant challenge for complete eradication. Many human bacterial infections, including chronic otitis media, chronic sinusitis, native valve endocarditis, and chronic airway infections in cystic fibrosis patients, are caused by virulent biofilms. The fabrication of efficient therapeutic techniques to manage biofilm infection remains a formidable task [127]. However, Zhao et al. have introduced a potential game-changer-liposomes triggered by near-infrared light and heat [127]. These liposomes can effectively combine photothermal and antibiotic therapies to eradicate Pseudomonas aeruginosa biofilm. Thermal-sensitive liposomes possess a positive charge and small dimensions and can infiltrate the biofilm microchannels, facilitating the targeted discharge of payloads at the diseased site. The liposomes exhibit stability at 37 °C and liberate over 80% of the antibiotics when the temperature surpasses 45 °C. The biofilm dispersion rate achieved 80%, representing over sevenfold augmentation in comparison to the surplus antibacterial pure solution. This indicates that the site-specific discharge of antibiotics and photothermal co-therapy significantly enhance the effectiveness of antibacterial treatment. In vivo studies using medicated liposomes for treating *P. aeruginosa*-induced abscesses demonstrated remarkable therapeutic efficacy. The study also revealed that photothermal therapy induced the upregulation of bcl2-associated athanogene 3, which protects healthy tissue from heat-induced impairment. Therefore, the use of near-infrared-triggered nanoformulation holds significant promise in augmenting the effectiveness of antibacterials via thermos-activated drug discharge and photothermal therapy [127].

3.3 Non-phospholipid liposomes

3.3.1 Niosomes

Niosomes (Fig. 10) are vesicular systems consisting of nonionic surfactants and lipids. They are engineered to transport drugs to targeted locations in the body. Niosomes have numerous merits over conventional liposomes, such as being non-toxic, highly reproducible, non-immunogenic, cost-effective, easy to scale up, and easily modified on their surface. Additionally, niosomes are stable over extended periods and under various conditions, which helps overcome liposome

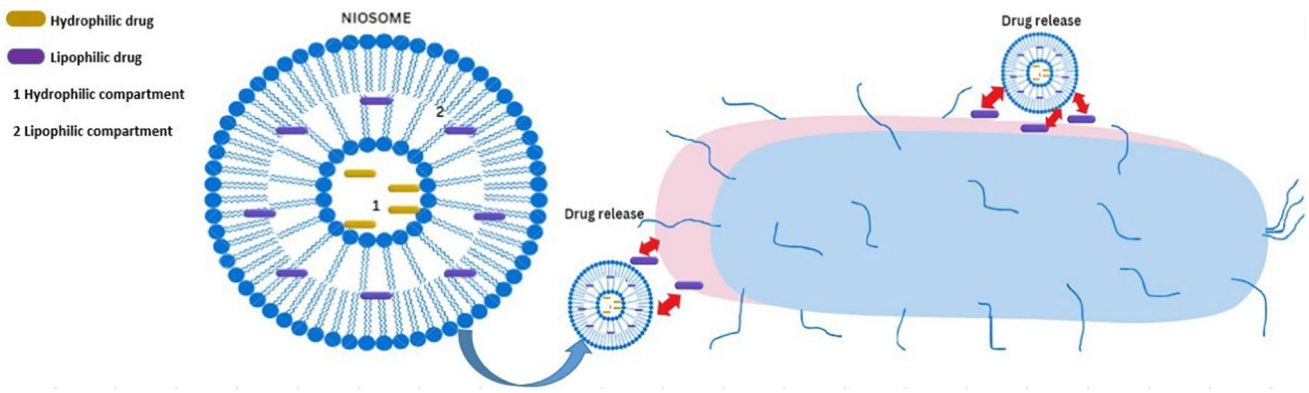


Fig. 10 A schematic illustration of a medicated noisome and its action on bacteria. The hydrophilic pharmaceuticals were encapsulated in the polar portion (1) and hydrophobic active agents in the apolar part (2). The encapsulated medicines were released and begins to act once the nano system engages with the microbe [130]

limitations. These systems' improved encapsulation efficiency, extended shelf life, stability, and regulated or sustained drug delivery capability enhance their bioavailability [128, 129].

Niosomes consist of nonionic surfactants like Tween, Span, and Pluronic L64, as well as lipids like cholesterol and shea butter. The typical concentration range for surfactant/lipid utilised to prepare niosomes is 10–30 mmol/L (1–2.5%, w/w). Modifications in the surfactant-to-water ratio in the hydration process might influence the form and characteristics of the resultant niosomes. As the surfactant/lipid concentration rises, the concentration of drug that may be enclosed also increases, enhancing the viscosity. Niosomes, composed of non-ionic surfactants, derive their name from this characteristic and are non-toxic due to the presence of these surfactants. Cholesterol is vital for enhancing the structural integrity of niosomes by providing mechanical stiffness to the vesicles. It also improves the efficiency of encapsulation and reduces the leakage of substances from the vesicles. These findings have been supported by studies conducted by El-Ridy et al. [131], Bhardwaj et al. [132], and Aparajay and Dev [128]. Niosomes can be administered by many modes of transport, including oral, parenteral, transdermal, ophthalmic, and pulmonary. Their morphology, dimensions, and encapsulation are altered by manipulating factors such as cholesterol concentration, surfactant type, additives, proportion, or synergistic use. While the niososomal delivery technique offers various benefits, the stability of the water suspension of niosomes may be compromised due to the potential hydrolysis of the drug. Drug release from the entrapment site and the production of noisome agglomerates may also be problematic [132–134]. Niosomes are formulated using certain chemicals that induce charge. These molecules produce an electric charge on the surface and keep the niosomes stable by repelling each other due to electrostatic forces, thereby preventing them from merging. Examples of compounds that induce charge include diacetyl phosphate (with a negative charge), phosphatidic acid (negatively charged), and stearyl amine (positively charged) [132].

Several infectious diseases go untreated because there is inadequate treatment available, the dosing frequency is not appropriate, the therapeutic window is narrow, or the half-life of the drug is short. Fungal and viral infections are poorly treated due to insufficient targeting and proper dosing, leading to serious patient compliance issues and side-effects [128]. Managing fungal infections poses a complex challenge for doctors due to the need for ongoing and prolonged treatment, which can result in liver toxicity, kidney toxicity, eye toxicity, and other adverse effects [128]. Various medication formulations are available, but their effectiveness is limited due to their toxicity and low capacity to pass through the skin [135]. The targeted formulation has become necessary for the long-term treatment of fungal infections. In this context, functionalized niosomes are more effective in reducing toxicities by generating sustained or controlled release formulations [128]. A vesicular carrier, such as the noisome, delivers substances through the skin and into the bloodstream [136]. Niosomes can persist in the bloodstream for a prolonged duration, resulting in a regulated release preparation that is advantageous for medications with quick clearance and shorter half-lives. This leads to less toxicity [133].

El-Ridy et al. [131] created niosomes containing nystatin (NYS) to combat *Candida albicans* parenterally in neutropenic patients. The authors altered the lipid content of the formed niosomes (Span 60 or Span 40 and cholesterol) by incorporating positive and negative charge-inducing compounds, Stearylamine and dicetyl phosphate. Niosomes with neutral and positive charges exhibited the highest encapsulation efficiency. The neutral and negatively charged NYS niosomes exhibited a gradual, sustained release profile. These niosomes showed improved antifungal effects by delivering a more significant drug concentration to essential organs. Additionally, they minimized the harmful effects of nystatin on the kidneys and liver when tested in living organisms [131].

Leishmaniasis is an infectious disease transmitted by a vector caused by a single-celled parasite called Leishmania [137]. At present, there is no available vaccination for the inhibition of leishmaniasis [138]. Leishmaniasis is one of the overlooked diseases that have few treatment options available. Scientist and global health organizations are compelled to explore novel approaches to fight and regulate this deserted disease due to factors such as high drug toxicity, lengthy treatment duration, parasite resistance, expensive therapy, challenging route of administration, co-infections like HIV/Leishmania spp., limited range of effective drugs (such as pentavalent antimonials, amphotericin B and formulations, and miltefosine), and insufficient investment in the discovery and development of new medications [139]. Leishmaniasis treatment will be revolutionised by nanotechnology. Liposomal amphotericin B has been permitted by the US Food and Drug Administration (FDA) as an effective therapy for Leishmania, replacing conventional Amphotericin B deoxycholate. However, this nanoformulation has some drawbacks, such as the need for varying doses subjected to the species of Leishmania and the geographical region, as well as its high cost [139, 140]. Niosomes offer a compelling alternative therapy for leishmaniasis [140].

Mostafavi et al. [140] created a niosomal drug delivery system combining Amphotericin B and selenium for the advanced *Leishmania tropica* (*L. tropica*) treatment. Utilizing advanced in vitro experiments, the niosomes containing a combination of medications had a notable inhibitory impact on the parasite compared to the mere solution of the

combined drugs (Amphotericin B and selenium). The niosomal formulation exhibited a markedly more significant inhibitory impact on the promastigote and amastigote forms of *L. tropica* than the basic combination form. Interleukin (IL)-10 exhibited a considerable drop, although the levels of IL-12 and metacasoase, as Th-1 activators, demonstrated a significant increase ($p < 0.001$). The research demonstrated the stability and effectiveness of niosomes as carriers for drug combinations. Niosomes were shown to be easily producible and cost-effective and showed promising results in suppressing both extra- and intra-cellular forms of *L. tropica*. This makes them a superior formulation compared to primary combination forms [140].

Mehta and Jindal's [141] innovative niosomal formulation of nevirapine (NVP) holds great promise for the management of acquired immunodeficiency syndrome (AIDS). Their research shows that the drug efflux can be effectively sustained, leading to a depot impact and reducing oscillations in drug discharge. This more adaptable and enhanced version of NVP could significantly enhance its therapeutic effectiveness and mitigate harmful systemic side effects, potentially increasing patients' quality of life and extending their existence time. The synthesised niosomes, as per Mehta and Jindal's [141] findings, serve as an adequate reservoir for the prolonged liberation of NVP, meeting the required standards of increased bioavailability and subsequently reduced dose.

Yadavar-Nikravesh et al. [134] examined the cytotoxicity and anti-HIV properties of Tenofovir-loaded PEGylated niosome coupled with TAT peptide. The inhibitory effects of drug-loaded nanoformulations on HIV-infected HeLa cells were assessed in vitro. The findings revealed that TAT conjugated niosomes (TAT-N) exhibited increased cytotoxicity, decreased anti-Scr HIV impact, and enhanced Tenofovir discharge profile compared to PEGylated niosomes (PEG-N). The transduction domain of the TAT peptide was found to enable the access of Scr HIV virions, which led to this result. As a result, the Tenofovir-loaded TAT conjugated noisome had a less inhibitory impact than the un-conjugated versions. Surface modification of niosomes with TAT peptide could enhance the drug release characteristics. The study found that PEGylation is more effective than TAT conjugation for delivering anti-HIV drugs [134].

TB is an infectious disease caused by Mtb, which infiltrates the lungs and initiates disease development. The pathogen can either remain dormant within the host's body without causing any symptoms, referred to as a TB infection, or it can become active and cause illness in the patient, known as TB disease. Combination chemotherapy is a fundamental approach for treating patients with TB. Multiple endeavours have been undertaken to utilise niosomes to deliver anti-TB medications for enhanced treatment results [142]. Niosomes have numerous benefits, such as superior drug encapsulation efficiency, effective penetration through mucus, and prolonged release at the desired location. Niosomes have demonstrated to be a superior substitue to traditional inhalation therapy, addressing the limitations of numerous medications [143]. Various niosomal formulations have been created to convey anti-TB drugs to achieve efficient TB treatment, reduce medicine dosage and toxicity, and improve patient compliance. These formulations specifically target macrophages, where TB bacteria reside [142]. Niosome carriers have effectively transported multiple anti-TB medicines to their intended locations. Several examples of these include.

Kulkarni et al. [144] demonstrated a groundbreaking approach in TB treatment by successfully developing a prolonged-release dual niosomal formulation. This innovative formulation combined lipophilic ethionamide and hydrophilic D-cycloserine, two drugs crucial in TB treatment. The nanoformulation, which underwent statistical optimisation using the Box-Behnken experimental methodology, was found to maintain stability for 6 months. Notably, the niosomes loaded with the two drugs exhibited a higher level of inhibition against *Mycobacterium* smegmatis compared to the combination of free medications, a promising result that underscores the potential of this method [144].

Eldehna et al. [129] have meticulously developed and created a potent compound, isatin–INH hybrid (WF-208), by combining isoniazid (INH) and 5-bromoisatin. This compound, specifically designed to target and effectively combat multidrug-resistant (MDR) and extensively drug-resistant (EDR) strains of M.tb, is the result of rigorous scientific investigation. WF-208 was explicitly engineered to selectively inhibit the DprE1 enzyme, a discovery made through an in silico molecular modelling investigation. The WF-208 chemical was then synthesized and encapsulated into niosomes, a method that enhanced its stability and enabled a prolonged antitubercular effect. After 3 weeks of incubation against H37Rv M. tb, WF-208-encapsulated niosomes demonstrated a prolonged antitubercular activity and a fourfold rise in the anti-mycobacterial property in contract to the pure compound (MIC of 1.9 vs. 7.8 µg/mL). This significant improvement in antibacterial effectiveness can be ascribed to the heightened contact between the cationic nanoparticles and the anionic cell walls of the bacteria. Moreover, the gradual liberation of the medication from the nanoformulation not only provides extended protection against degradation but also holds the promise of significantly improving the treatment of TB. By synthesizing a hybrid antitubercular compound and integrating it into nanosized vesicles, the authors have enhanced the antibacterial activity's stability, potency, and sustainability and opened up new possibilities in the

fight against this global health threat. As demonstrated by WF-208, this innovative approach shows great potential for revolutionizing TB treatment [129].

3.3.2 Sterosomes

Sterosomes are nanocarriers composed of liposomes that do not include phospholipids [146]. These vesicular systems are distinct from liposomes since they utilise monoalkylated amphiphiles instead of phospholipids (Fig. 11), as stated by Cui et al. in 2015. Sterosomes are vesicular systems mainly composed of single chain amphiphiles with large sterols, namely 50–75% cholesterol content. The word "sterosomes" was obtained from their significant cholesterol content [147]. Several studies have shown that combining monoalkylated amphiphiles, such as alkylated primary amines (e.g., stearylamine (SA), N-acylethanolamine, and cetylpyridinium chloride) or saturated fatty acids (e.g., palmitic acid, lauric acid, myristic acid, and stearic acid), with sterols (e.g., cholesterol (chol), cholesterol sulphate, and dihydrocholesterol) in specific ratios (25:75, 30:70, or 50:50) can lead to the creation of highly rigid liquid-ordered (LO) lamellar phases or large unilamellar vesicles (LUVs). These structures exhibit superior characteristics and functionality compared to traditional liposomes. Various researchers have reported these findings [146, 148, 149].

A critical feature of these vesicles is their sensitivity to pH, which allows for pH-activated release based on the protonated or unprotonated state of their non-phospholipid components [146]. The pKa value of monoalkylated amphiphiles can alter the pH-induced release of these advanced vesicles, while the properties of the sterol component affect the overall pH stability. Thus, by selecting single-chain amphiphiles with specified types and pKa values, sterosomes can be custom-designed to release active compounds at a particular pH for precise drug delivery targeting [150].

In their study, Nwabuife et al. [145] created stereosomes filled with antimicrobial agents, to address the resistance exhibited by *S. aureus* and Methicillin-resistant *S. aureus* (*S. aureus* and MRSA). Vancomycin was administered using sterosomes composed of stearylamine and cholesterol in a 1:2 ratio to eliminate MRSA and *S. aureus*. Following a 90-day testing period at different storage temperatures, these vancomycin-loaded sterosomes demonstrated exceptional physical durability and no indications of hemolysis. Approximately 80% of the vancomycin was gradually released from the sterosomes for 3 days. Compared to a sterile vancomycin solution, the drug-loaded sterosomes exhibited enhanced, superior, and more rapid bactericidal activity against the tested highly resistant pathogens. This study also showed that these drug-loaded nano vectors effectively reduced the MRSA mature biofilm. The intradermal application of vancomycin-sterosomes effectively eradicated MRSA in infected mice's skin, surpassing the efficacy of standard medication formulation [145].

Zhang et al. have successfully created a multifunctional sterosomal platform that can be used to cure infected bone deformities. This platform can mix therapeutic genes, small compounds, and pharmaceuticals, making it highly versatile. The equimolar ratio of cetylpyridinium chloride to 20S-hydroxycholesterol was used to create sterosomes. The antibacterial effects of the pure sterosomes, which were dose-dependent, were observed on Gram-positive and negative microorganisms. These effects were equivalent to the antimicrobial properties of pure cetylpyridinium chloride. These non-medicated nano vehicles efficiently eradicated the bacterial biofilms. The comparative investigation in this

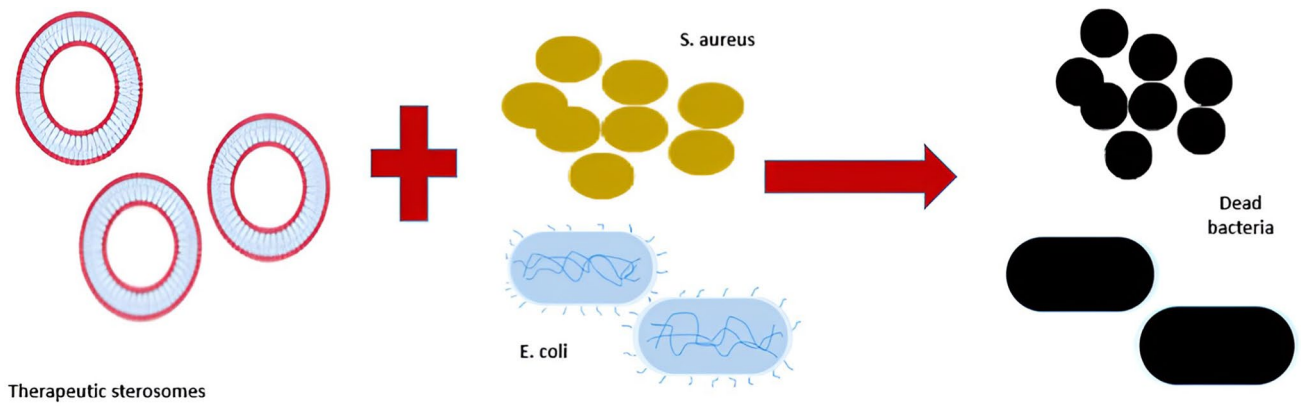


Fig. 11 A diagrammatic representation of the antibacterial activity of cetylpyridinium chloride sterosome on Gram-positive and Gram-negative bacteria [149]

work employed stearlyamine/20S-hydroxycholesterol sterosomes; however, only a tiny amount of evidence about their antibacterial ability was found [149].

Yang et al. [151], propose that cationic sterosomes can effectively treat bacterial infections in dentinal tubules. In order to develop sterosomes that can effectively address pulpal inflammation without active drugs, a combination of cholesterol and cetylpyridinium chloride was utilized as functional components. Cetylpyridinium chloride demonstrates inherent, wide-ranging antibacterial activity. The unmedicated sterosomes suppressed the progression of Gram-positive and -negative oral endodontic microorganisms and associated biofilms in a way dependent on the concentration. The synthesised sterosomes showed improved intrinsic ability to penetrate and diffuse across the dentine and pulp tissue in vivo without using mechanical instruments [148, 151].

3.3.3 Ufasomes

Ufasomes (Fig. 12) are enclosed lipid layered liposomes of unsaturated fatty acids that ensnared lipophilic medicines. Their composition consists of unsaturated fats such as oleic acid, sodium oleate, linoleic acid, and ionized soaps. These substances have a restricted pH range of 7–9, within which the fatty acid carboxylic acid moieties are organized as bilayer vesicles, with some fully ionised and others unionised. Fatty acid vesicles normally consist of two types of amphiphiles: non-ionic neutral molecules and ionised molecules (often called negatively charged soap). Vesicle stability is primarily regulated by the ratio between non-ionic neutral and ionic forms [152, 153]. The fatty acid vesicles possess fusogenic properties, resulting in a decrease in the transition temperature of the membrane. When lipid-filled vesicles come into contact with the lipid bilayers of the skin, they stick to the surface of the skin and promote the transfer of lipids across the outermost layers, known as the stratum corneum (SC). As a result, the vesicles release their contents through the interchange of lipids between the SC layer and the lipid carriers. Once they penetrate the stratum corneum and reach the dermis, they are eliminated by combining with fatty acids in the sebum that surrounds the hair shaft. Fatty acid vesicles are an appealing choice for delivering drugs specifically to the hair follicles [152].

Research has confirmed that vesicles containing fatty acid are the most efficient carrier for enhancing skin penetration across the stratum corneum [155]. The ability of ufosomes to boost skin permeability is mainly ascribed to the insertion of unsaturated fatty acids into the bilayer. This insertion induces a disturbance in the skin, leading to increased membrane fluidity, reduced viscosity of the mucous layer, and breakdown of tight junctions. Unlike conventional liposomes, which struggle to penetrate deep layers of the skin, ufasomes have demonstrated enhanced effectiveness in this regard [153, 156]. Fatty acids are abundant and cost-effective in comparison to other lipids. The production of ufasomes offers the additional benefit of being cost-efficient [153, 154]. The lipid vesicles were also employed for the intranasal delivery of active medicinal components [156].

The prevalence of superficial fungal illnesses caused by dermatophytes is substantial, impacting more than 35 million individuals worldwide. According to Bolla et al. [156], it ranks fourth in frequency as a source of infection. Fungal infections result in a mortality rate above 1.5 million individuals' annually worldwide [157]. Some known fungal pathogens that cause fungal infections are Candida, Aspergillus, Cryptococcus, Scedosporium, Zygomycetes, and other species. Clotrimazole, an imidazole antifungal drug with a wide range of effectiveness, is commonly employed to treat fungal infections [153]. Bolla et al. [153] developed clotrimazole-loaded sodium oleate-based ufosomes to address the limitations of traditional clotrimazole topical formulations, including low skin bioavailability, limited penetration, and inconsistent drug levels. Analysis of topical diffusion demonstrated that ufosomes resulted in a greater concentration

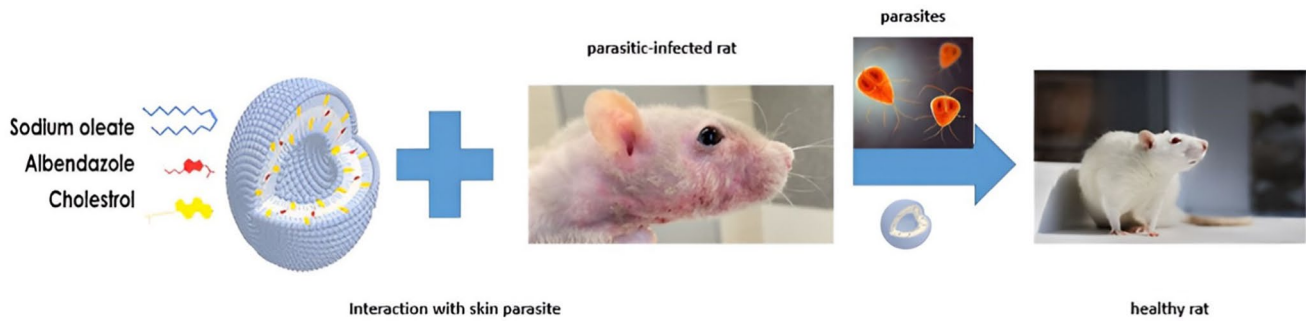


Fig. 12 An Albendazole loaded-ufasomal platform for the treatment of skin-parasitic infection in Wistar rat [154]

of the antifungal drug in both the epidermis and dermis of the skin in comparison to the commercially available Perrigo formulation. This study demonstrates that ufosomes can improve the topical bioavailability and targeted distribution of medicines. In summary, the findings showed that these vesicles can enhance the skin's absorption of clotrimazole. The primary challenges in treating fungal infections are the resilience of the fungi to current antifungal medicines and the limited effectiveness of these drugs in penetrating the infected areas.

Hashem et al. [158] effectively developed ufosomes using oleic acid as a base to enhance the capability of itraconazole (ITZ) to permeate tissues and improve its therapeutic effectiveness. The microbiology study verified that the ITZ-loaded ufasomes can hinder *Candida albicans*' secretion of phospholipase and proteinase. Additionally, they have a downregulating action on the immunomodulatory IL-1β and TLR-4. This indicates that the suggested formulation has potential for treating *C. albicans* infections.

Bhattacharya [155] created ufasomes containing terbinafine hydrochloride, which are glyceryl oleate-based and designed to effectively treat fungal infections that target the deeper layers of the skin. The rats afflicted with cutaneous candidiasis, employed for the in vivo study, demonstrated that the ufasomes exhibited effective antifungal activity after 5 days. The nanoformulation demonstrated enhanced local effects, more excellent penetrability, and lower dose and toxicity [155].

3.3.4 Novasomes

Novasome is a modified version of liposomes that addresses various challenges associated with liposomal drug delivery systems. It features a seven-bilayer membrane that can accommodate both water-soluble and insoluble pharmaceuticals. The composition blends surfactant, cholesterol, and free fatty acids, enhancing vesicle medication administration properties [159].

Novasome improves the composition of traditional liposomes, ufasomes, and niosomes, which typically consist of cholesterol, free fatty acids, and polyoxyethylene fatty acids [159–161]. This mixture is similar to a blend of ufasomes, composed of unbound fatty acids, and niosomes, composed of a nonionic surfactant. This mixture yields an exceptional medication delivery system with outstanding features. The entrapment efficiency of this product is exceptional, resulting in improved medicine delivery. The Novasome micro vesicles possess intrinsic stability and are specifically designed to maintain stability within a pH range of 2–13 and a temperature range spanning from liquid nitrogen temperatures to temperatures exceeding the boiling point of water. Novasome provides a mechanism for continuous and controlled release of substances. The Novasome bilayers lack a well-organized array configuration. They have openings, or channels, that allow encapsulated components to pass through them. The encapsulated components within the core move laterally between each bilayer by a series of random jumps, resulting in the movement of channels in the bilayer. This results in the liberation of active substances from the bilayers via the aqueous suspension that separates them. The surface of microvesicles might possess a net negative charge, a net positive charge, or no net charge, ultimately determining their activity level. For instance, the microvesicles with a positive charge can bind to the skin, mucous membrane, or hair with a negative charge. Novasome vesicles, with their unique structure, offer a prolonged release mechanism that enables a regulated release of the active substance. The active ingredient's storage stability and stability are significantly enhanced because the active component is more securely enclosed within the core before usage. This results in a promising potential for heightened efficiency and effectiveness in delivering the active substance [160], sparking optimism about their role in drug delivery.

Mosallam et al. [162] showed that terconazole's effectiveness was improved when it was loaded in a novasome compared to a noisome. Albash et al. conducted research that demonstrated the exceptional properties of novasome in encapsulating fenticonazole nitrate. The study also revealed that novasome has a strong ability to combat fungal infections, specifically tinea corporis, when applied topically [161].

Zakaria et al. [163] produced a formulation of luteolin (LUT)-loaded novasomes to promote its distribution to the skin's surface and increase its ability to fight against MRSA in severe deep skin infections. Formulation F2 in this investigation showed improved antibacterial efficacy with reduced minimum inhibitory concentrations against a group of MRSA clinical isolates in contrast to LUT solution. In addition, the F2 formulation demonstrated superior anti-virulence properties by efficiently averting the growth of biofilms and decreasing the activity of α-hemolysin in MRSA isolates. Additionally, it exhibited enhanced biosafety by evaluating cytotoxicity on human skin fibroblasts (HSF). Ultimately, when evaluated in a live mouse model of skin infection, the F2 formulation and a marketed fusidic acid formulation effectively decreased the number of microorganisms in infected skin lesions opposed to the negative control and pure LUT solution-treated groups.

Fungal eye infections, while less common than viral and bacterial infections, are highly perilous as they have the potential to result in blindness. The incidence of fungal ophthalmic infections has significantly grown because of the increasing number of individuals with weakened immune systems resulting from viral infections, chemotherapy, transplantation procedures, and anti-cancer treatments [164]. Encapsulating antifungal agents in lipid vesicles is a promising method to enhance the cornea's permeability, prolong the medication's presence in the eye, and enhance the solubility of the drug. This approach can lead to successful treatment by increasing the drug available in the eye and reducing its toxicity [164]. Ahmed et al. [165] created fenticonazole nitrate (FTN) enclosed novasomes to elevate the medicine's capability to permeate the cornea and boost its antifungal effectiveness in treating ocular candidiasis. The effectiveness of the novasomal formulation was verified through an in vivo investigation of the absorption of the formulation by the cornea and a test on its susceptibility. The scientists concluded that the drug-loaded novasome has been deemed safe based on an in vivo eye irritation experiment and corneal tolerance test. Additionally, it has demonstrated increased corneal permeability (527.98 μg/cm^2), resulting in enhanced antifungal efficacy. This study's findings have substantiated the novasomes' efficacy in enhancing the penetration of fenticonazole nitrate through the cornea and its antifungal properties [165].

4 Conclusions and future outlook

The relative success of liposomes as a drug carrier has renewed interest in the research and development of antimicrobials and vaccines to treat infectious diseases. Conventional liposomes are limited by several factors and has prompted a shift towards the discovery and emergence of more advanced liposomal delivery strategies to minimize or eliminate these limitations and optimally treat infectious diseases. The challenges of treating infectious diseases are confounded by antimicrobial drug resistance, non-specificity and poor drug targeting with harmful side-effects. The use of advanced liposomal formulations can change the clinical fate of chronic infectious diseases by providing controlled and targeted drug delivery, immunomodulation, and intracellular uptake due to their distinct features. The propensity of advanced liposomes to effectively deliver genetic material and intracellular delivery of antimicrobial drugs makes a substantial advancement in the chemotherapy of infectious diseases. There is a strong impetus to expand research into the use of cationic and magnetic liposomes in the fight against infectious diseases as efficient targeting strategies. Furthermore, immunomodulatory agents can facilitate the enhancement of the host immune response against pathogens (i.e. host-directed therapy). Adopting a tailored immunomodulatory approach will assist in targeting the pathogenic microorganisms in conjunction with the host immune system to fortify host defenses. Future studies on combinational treatments such as co-encapsulation and co-delivery of therapeutic agents, immunomodulators, and diagnostic agents within advanced liposomes will expand the utility and impact of liposomal technology.

Author contributions The concept for this work was conceived by NIO based on one of the DiscoverNano Journal's advertised issues. Professor YEC authorized it, and all the authors agreed to contribute. Thus, the abstract, introduction, conventional liposomes and their limitations, stealth liposomes, biomimetic liposomes, immunoliposomes, fusogenic liposomes, conclusion, and future perspective were all written by NI Okafor. OAO worked on the modified liposomes (niosomes, sterosomes, ufasomes, novasomes) and stimuli-responsive liposomes (pH liposomes, light-sensitive liposomes, thermal-sensitive liposomes). Before final submission, Professor YEC, proofread and edited the complete manuscript, which was then corrected and approved by all the writers for final submission.

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Data availability Not applicable.

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Declarations

Competing interests The authors declare that they have no competing interests.

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