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A review on liposome as a drug delivery system for antibiotics

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Abstract

Antimicrobial medications are essential for both treating and preventing bacterial infections. The growth and spread of resistant bacteria pose significant obstacles to the current management of bacterial diseases, notwithstanding the early effectiveness of antibiotics. It is imperative to take action to prevent and manage antibiotic resistance in order to prevent a potentially catastrophic clinical collapse. World Health Organisation (WHO) and national health authorities have mostly recommended action plans to limit the use of antibiotics while enhancing hygiene and drug disposal practices. Our goal in writing this review is to discuss how well antibiotic-encapsulated liposomes work as a treatment for bacterial illnesses.

Keywords: Liposome; Antibiotics; Bilayer Vesicles; Antimicrobs; Phospholipid Bilayer

1. Introduction

Liposomes are bilayer vesicles that are used as medication delivery systems (1). The first closed bilayer phospholipid systems, called liposomes (2). The liposome, a revolutionary delivery system, has shown promise for pharmaceutical delivery (3). Since the early 1960s, the mechanism of action of antibiotics has been defined, with their pharmacological target serving as the basis for classification (4).

Antimicrobials are indispensable pharmaceuticals essential for treating bacterial infections. However, for decades, the use of antibiotics in animal husbandry, agriculture, and clinic settings has put tremendous selection pressure on bacterial species (5). Antimicrobials are just one more of the obstacles that bacteria must overcome in order to thrive on Earth; humans and their products represent a tiny portion of the history of microbial life. Furthermore, new findings have led us to believe that bacteria are more than just observers of their own success in adaptation. Antibiotic resistance in bacteria can develop in a number of ways, including changes caused by mutations in antibiotic targets, changes to cell permeability and efflux, and the horizontal transfer of resistance genes (6). They are beneficial to the care of animals and the production of wholesome food for humans from animal sources (7). The main goal of this review is to demonstrate the advantages of liposomes as antimicrobial agent carriers, as well as their ability to eliminate infections and defeat antibiotic resistance (5). This review addresses new therapeutic options aimed at addressing antibiotic resistance and extending the useful life of antibiotics, as well as current antibiotic therapy in the context of growing multidrug resistance.

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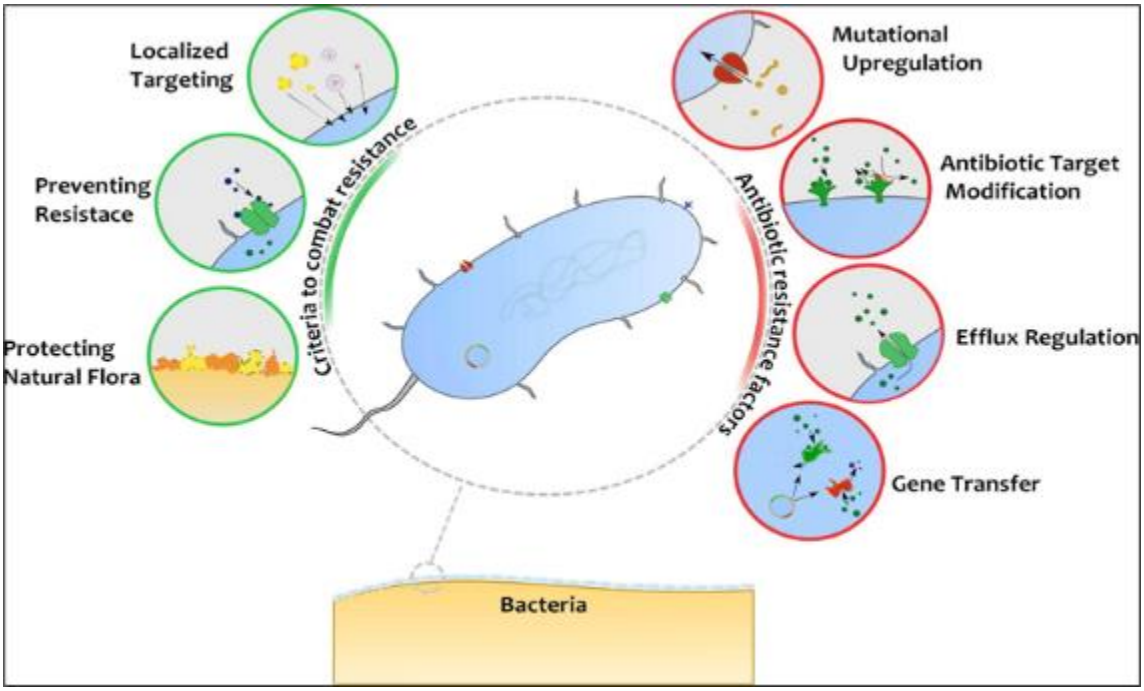

Figure 1 Antibiotic Resistance (8)

The global danger of antimicrobial resistance (AMR) to human, animal, and environmental health is becoming increasingly concerning (9). We use freeze-drying and freeze-thawing processes to freeze liposomes during formulation and post-formulation, respectively (10). The product's intended usage has changed in two primary areas during its development life narrative (11). Despite prolonged incubation of the liposomes, no visible drug-free liposome lipid entered the fungal cytoplasm (12). It is imperative to take action to prevent and manage antibiotic resistance in order to prevent a potentially catastrophic clinical collapse. The World Health Organization (WHO) and national health agencies have mostly recommended action plans that limit the use of antibiotics while enhancing hygiene and drug disposal techniques (13).

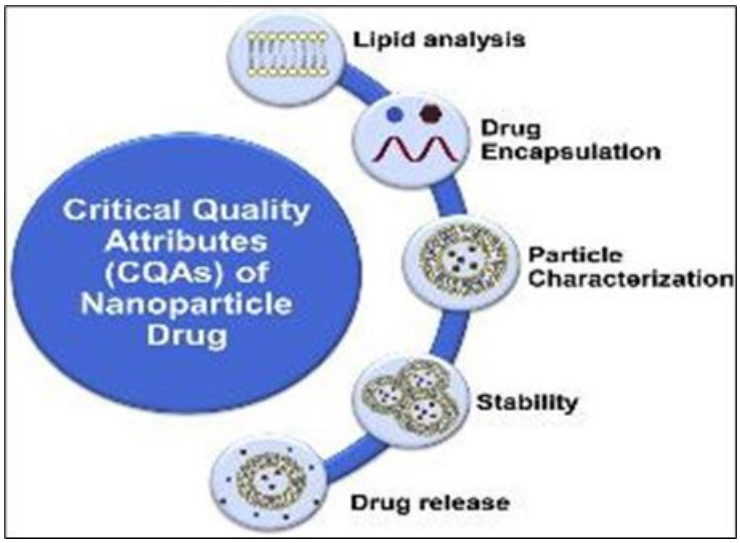

Figure 2 Analytical Characterizations of Liposomes (23)

It is possible to precisely control the shape of the liposome composition to promote fusion or adsorption onto the microbial cell membrane. Similarly, the infectious agent's properties can alter the surface of vesicles (14). The following characteristics identify a new antibacterial drug: A new antibacterial drug has these features: (i) it works in new ways or binds to new target sites; (ii) it interacts with a new target; and/or (iii) it changes biochemically to make a pathogen that was previously resistant to it susceptible again (15, 16, 17). Drug carriers, such as liposomes, can alter the

pharmacokinetic and bio distribution profiles of drugs, leading to the creation of novel treatment modalities (18). Liposomes are spherical vesicles with an aqueous core surrounded by one or more concentric phospholipid bilayers (19). By altering the lipid content, liposomes can become both biocompatible and biodegradable (e.g., at a specific pH and temperature) (20). In vitro susceptibility testing, which determines whether antibiotics can kill the pathogen, is a standard component of infectious diseases, particularly those caused by bacteria or fungi (21). Antibiotics have revolutionized medicine since the 1928 discovery of penicillin, and they are necessary medications that can save lives (22).

2. Structure and property of Liposome

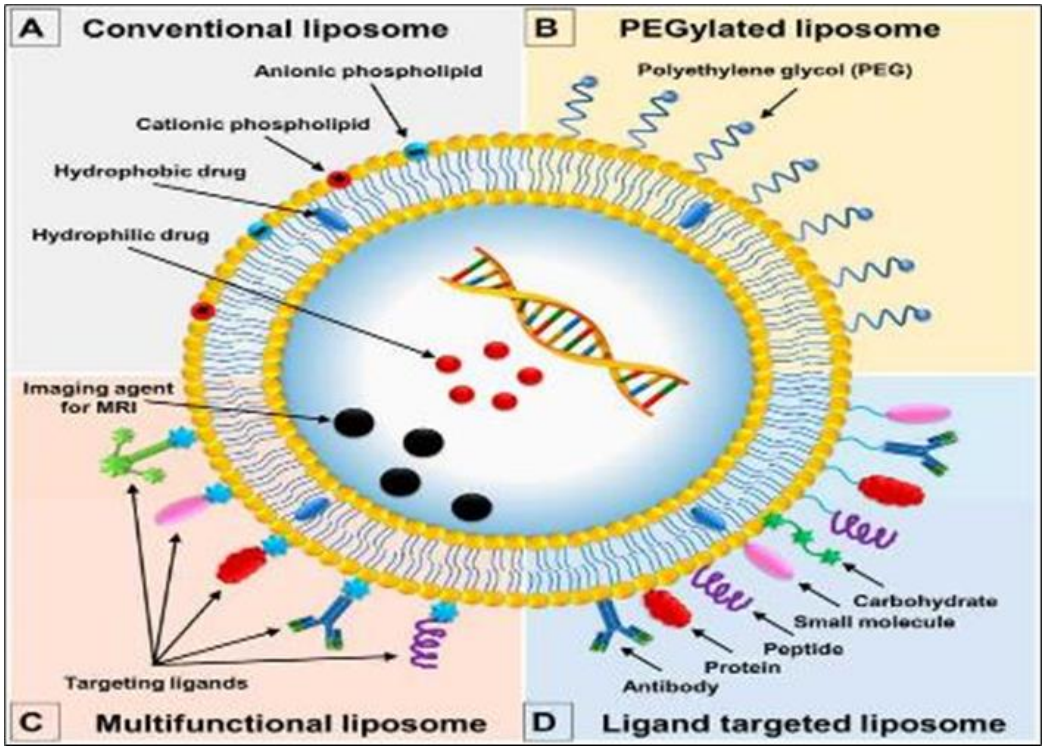

Figure 3 Schematic representations of different types of liposomal drug delivery systems (5)

As carriers, liposomes have many benefits, such as a membrane structure similar to a cell, high biocompatibility, low immunogenicity, protection of the medication or active group, longer drug half-life, lower toxicity, higher efficiency, and more (24). Unlike other nanoparticles, liposomes can contain both hydrophilic drugs in the aqueous compartment and hydrophobic drugs inside the lipid bilayer. This allows for the inclusion of smaller amounts of a greater number of drugs (25). The most popular and well-studied nanocarrier for targeted drug delivery is liposomes. They have improved therapeutics for many biomedical uses by making therapeutic chemicals more stable, getting rid of things that stop cells and tissues from absorbing them, and making it easier for compounds to get to where they need to go in living things (26). Researchers have also employed colloidal particles made of biodegradable polymers, which could have promising future uses in antimicrobial chemotherapy. The method of delivery of both types of carriers influences there in vivo behavior and, in turn, their therapeutic potentia (27). These carriers serve as a key component of effective treatment administration and efficacy (28). One of the most promising and extensively researched nano-vehicles for delivering and carrying antimicrobial drugs is liposomes (29). The nature of the phospholipid molecules used to form the liposome preparation determines liposome stability. As temperature increases, pure phospholipid bilayers are known to transition from a gel to a liquid crystalline state (30).

Advantages of Liposomes (5, 31)

- Target delivery
- Decreased toxicity
- Protection against metabolic breakdown
- Controlled and prolonged release
- Extended plasma circulation

- Enhanced bactericidal activity
- Improved protection and antibiotic biodistribution
- Affinity for selective biofilm targeting
- Enhanced ability to distinguish between bacterial strains that are extracellular and intracellular

3. Composition of Liposome

Liposomes are the antimicrobial medication delivery nanosystems that have undergone the most research and development. Their spherical structures, which range in size from 0.02 to 10 μm, are composed of phospholipid bilayers encircling an inner aqueous space (31). With over fifteen liposomal medicines on the market that have received FDA approval, liposomal formulations provide a significant platform in nanomedicine. However, liposomal formulations and production, along with other nanoparticle-based delivery systems, are naturally complicated and linked to a lot of different dependent and independent variables. This makes experience optimization a very time-consuming process (32). Initially, antibiotics were considered "wonder drugs" due to their introduction at a time when the only available treatments for severe bacterial infections were surgical drainage or natural recoveries. (33). Researchers have studied liposomes more than any other carrier system due to their diverse shapes. Phospholipids form sphere-shaped liposomes, which can transform into a water solution by forming a hydrophilic space within them. Bangham and colleagues first described liposomes as small, spherical vesicles containing phospholipids, cholesterol, non-toxic surfactants, and even membrane proteins approximately forty years ago. Investigations by this group led to the idea that liposomes, known for delivering a range of chemicals in the core region, could serve as delivery systems (34). Liposomes are beneficial for drug delivery because they can hold both water-loving and water-hating medicines, as well as being biocompatible and biodegradable (35). Furthermore, liposome preparation processes used in laboratories do not easily convert to large-scale production, which may delay the development and adoption of new liposomal systems. The goal is to foster progress and creativity in the liposome production process (36). Adding polyene antibiotics to liposomes improves their bioavailability, therapeutic index, and availability at the infection site. This is mostly because circulating monocytes and macrophages take up the liposomes and transport them to the infection site (37).

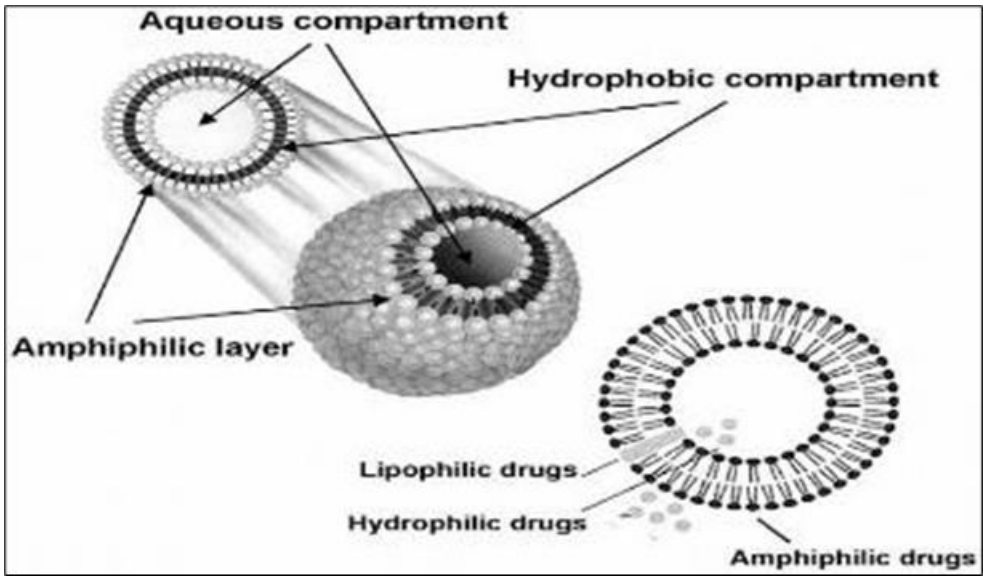

Figure 4 Innovative Drug Delivery Systems for Natural Compound Administration (34)

4. Advantages of Liposomes as Antibiotic Carriers

Advancements in liposomal formulations have facilitated the creation of promising antibiotic delivery systems that have the potential to address important concerns in the management of infectious illnesses (5). According to a number of studies, liposomal encapsulation increases the safety and stability of antibiotics. It also results in more suitable pharmacokinetic and pharmacodynamic profiles by extending the time that an antibiotic is in the bloodstream and allowing for more precise targeting of the infection sites through a variety of administration methods (31).

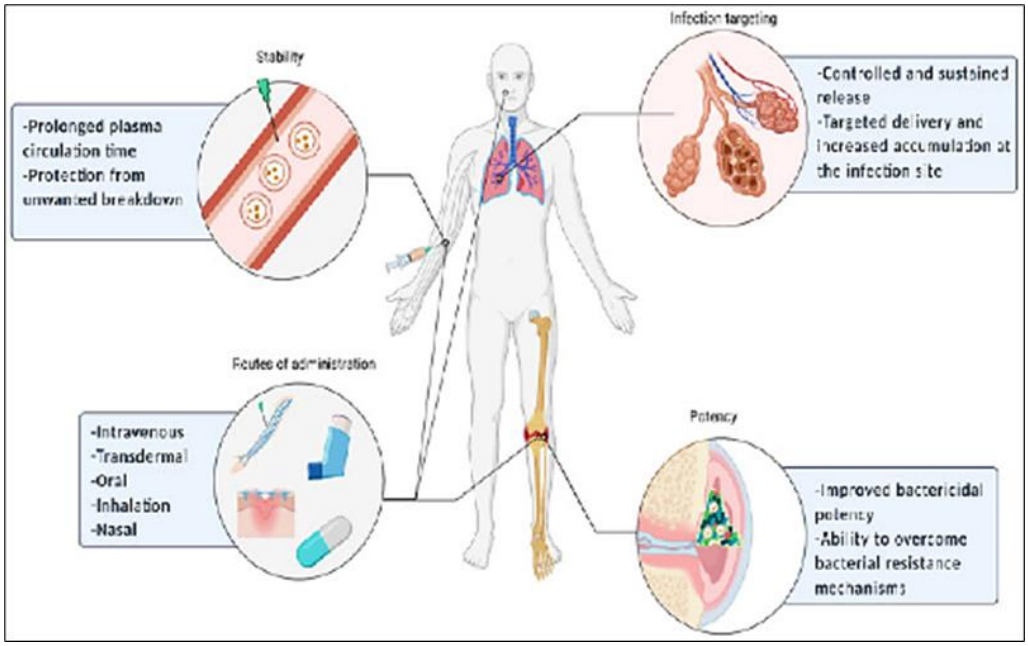

Figure 5 Depicts the primary advantages of liposomes as antifungal carriers.(5)

4.1. Stability

4.1.1. Controlled and sustained release of antibiotics

Beta-lactam antibiotics frequently serve as antibacterial medications when treating critically ill patients. There are a few things about critically ill patients (like sepsis, kidney failure, or better renal clearance and renal replacement therapy) that might change how beta-lactams work in their bodies compared to patients who are not critically ill (38). In comparison to fractionating regimens, higher antibiotic doses are more effective at eliminating and avoiding resistance strain selection (27). Antimicrobials are among the most misused drugs worldwide. It is important to correctly identify infections, know the difference between empirical and definitive treatment, think about switching to low-cost, narrow-spectrum oral agents as soon as possible, know the specific properties of antimicrobial agents, such as how they work and what effect they have on the infection site, know how the host's characteristics affect antimicrobial activity, and finally know how antimicrobial agents hurt the host (39).

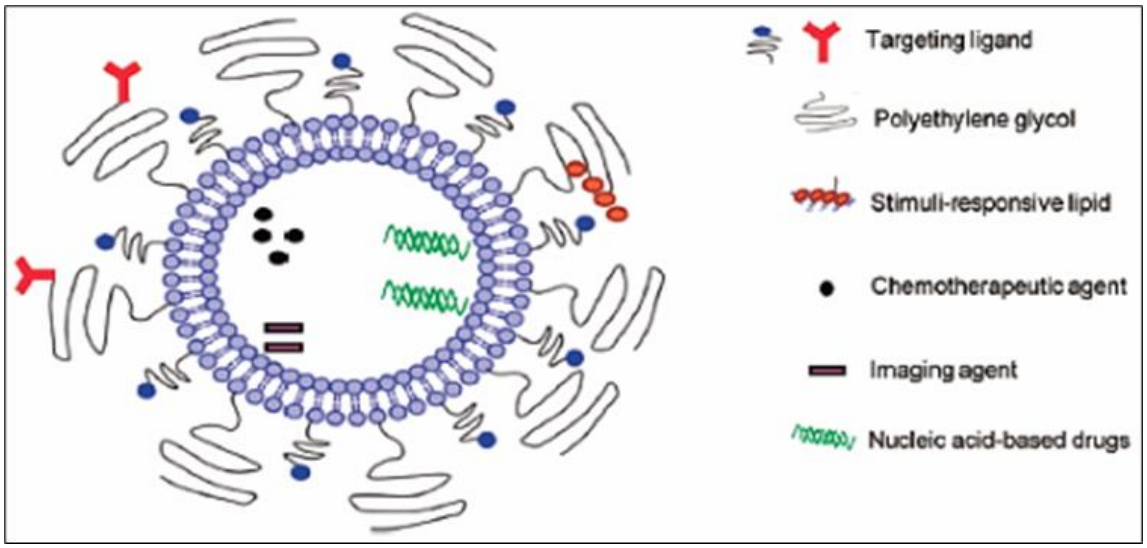

Figure 6 Schematic picture of a multifunctional liposome (40)

The severe difficulties in treating bacterial infections and the rise in bacterial resistance, the use of liposomal antibiotic carriers may be helpful; however, one should also consider the high expense of liposome manufacturing and treatment (35).

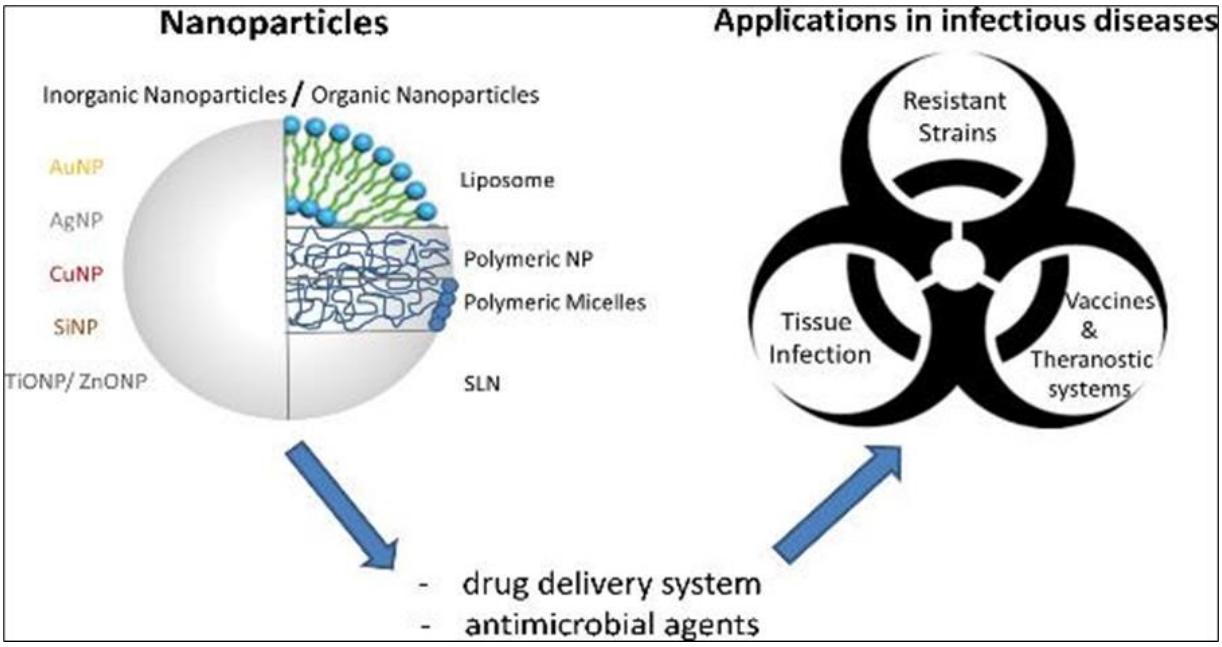

Figure 7 Nanoparticles (41)

The ability to control the released of the entrapped antibiotic is a significant benefit of using liposomes to contain antibiotics (42).

4.1.2. Prolonged Plasma Circulation Time

Certain antibiotic families, such as β-lactams, have higher serum protein binding characteristics, which affect the plasma concentration of free antibiotics and reduce their antibacterial activity (43). The biodistribution of medications has a significant impact on patients' quality of life and survival. It is difficult or impossible to provide therapeutic drugs locally for many disorders, including metastatic cancer; thus, drug transport through the circulatory system is necessary (44). The mononuclear phagocytic system (MPS) clears certain liposomes, including synthetic or natural phospholipids, from the body more quickly and tends to collect in the spleen and liver (45). Changing the liposome's physicochemical properties, like its size and surface charge, can make its systemic circulation last longer. Liposomes that are neutral or small have a longer circulatory half-life (46). This tactic lengthens the duration that blood circulates in the circulation, improves liposome stability, and minimizes contact with plasma proteins and macrophage recognition (47).

Liposome encapsulation offers protection against unintended enzymatic degradation and chemical or immunological deactivation (48). Biocompatible hydrophilic polymers, such as polyethylene glycol (PEGylated liposomes), can coat them to prevent MPS uptake (49). Antimicrobial agents can potentially enhance the efficacy of liposomal formulations. It is well established that liposomal encapsulation works well to increase drug accumulation at disease sites, decrease drug toxicity, and extend the period that a drug is in circulation following intravenous injection (50, 51). Liposome-encapsulated antimicrobials may have better pharmacokinetics and pharmacodynamics, as well as less toxicity, compared to traditional formulations (51).

4.1.3. Infection Targeting

The ability to target a specific area, such as a specific tissue, organ, or even pathogenic bacteria, is one of the best things about liposomes for delivering antimicrobial drugs (52). There are liposomal preparations for mycobacteria besides tuberculosis and P. aeruginosa (53). Additionally, researchers are exploring the idea of combining two antibiotics into a single liposomal formulation to enhance the effectiveness of treatments for MDR-caused lung infections (54). One therapy option that is gaining more attention is the aerosol delivery of antibiotics. Advances in drug nanotechnology lead to the creation and integration of novel compounds with aerosol production systems (55). Locally, people prefer to use antimicrobial medications to prevent and treat chronic wounds that do not heal, such as pressure ulcers, diabetic wounds, and vascular wounds (56). Spray drying technology atomizes a liquid liposome suspension or dispersion into

a stream of hot air, collecting the resulting dry powder (57). Even though the skin and the eyes are easily accessible, not all medications included in creams, ointments, or suspensions deliver the right amounts due to issues with drug instability or the body's defense mechanisms. Furthermore, the rise in antibiotic-resistant bacteria, such as MRSA, that cause skin infections can spread to deeper soft tissues, resulting in diseases like cellulitis, abscesses, or even fasciitis necrotizing (58).

In order to overcome this problem, liposomes that ensure an uninterrupted release of the antibiotics in aerosol formulations are currently under development (59). Because nano-DDSs can maintain drug release and prevent drug degradation, they have enormous potential to improve drugs therapeutic efficacy. People are developing and using unprecedented numbers of nano-DDSs containing medicinal substances to promote skin regeneration and wound healing. These include liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures, and nanohydrogel (60). A single dose of liposome-encapsulated silver sulfadiazine significantly reduced the number of bacteria compared to untreated controls and to a lesser extent, repeated applications of free medication (61).

In fact, topical liposomal formulations are already available on the market (62). Scientists have found that liposomes tend to gather at infection sites and interact directly with bacteria, depending on their physical and chemical properties, especially the charge on their surface (63). Under normal circumstances, pathogenic bacteria have a negatively charged cell wall (64). It is possible to create liposomes that release the encapsulated substance in a form that is dependent on pH or temperature (65). When heated locally, temperature-sensitive liposomes can release the included medicine (66). Liposomes release integrated medications at temperatures higher than the lipid bilayer's melting transition temperature (67). Targeting ligands, like antibodies, aptamers, proteins, or antibody fragments, attach to the surface of liposomes and form a specific bond (68). Target cells recognize these specific surface receptors, enabling the local administration of the liposomal formulation (69). This tactic is especially intriguing for medicines like vancomycin, whose nephrotoxicity restricts their therapeutic utility (70, 71). This method can create liposomes that go after difficult-to-treat Listeria monocytogenes or Mycobacterium tuberculosis infections that occur inside cells. Liposomes with lysostaphin attached to their surface were more effective at binding and killing bacteria than liposomes that were not attached (72). Another major problem in treating bone infections is their low success rate, which necessitates the long-term use of antibiotics (73). Therefore, a compelling strategy is to link localized antibiotic administration to nanoplatforms (74). Indeed, several methods of administering medication for this condition involve the implantation of medical devices (75). However, the authorization for these devices only extends to the second stage of a surgical revision (76). Once again, it is possible to create liposomes that can target bone (77). Because calcium phosphate is biocompatible and can attach to bone tissue, coating drug delivery systems with it or its derivatives is a common practice (78). An intravenous injection of free or liposomal gentamicin yielded no therapeutic effect (79). Another pathology that warrants special consideration when it comes to antibiotic distribution is bacterial meningitis (80). The high death rate and neurological aftereffects experienced by those who survive make it one of the most serious infectious diseases in the world (81). S. pneumoniae and Neisseria meningitidis are the two most prevalent bacterial agents; however, other microorganisms can also cause it; the former is responsible for more than two-thirds of cases in Europe and the USA (61%) (82).

The inadequate penetration of antibiotics through the blood-brain barrier (BBB) is a significant problem in the clinical management of meningitis treatment (83). Essentially, 98–100% of large-protein medicines and >98% of small-molecule medications do not cross the BBB (84). However, for most antibiotics, the resulting rise in toxicity levels renders this strategy inappropriate and, in some situations, impractical (85). Moreover, a pneumococcus that is resistant to multiple drugs could complicate matters. This could make it take longer to give the right antibiotic, which could result in a poor course of treatment (86). In this case, liposomes and polyanions at the BBB interact with each other electrically, which leads to endocytosis through adsorptive mechanisms (87). Researchers have observed the maximum uptake of positively charged liposomes into brain parenchyma, including glioma tissue (88). Researchers have investigated the use of ligand-targeted liposomes to target brain endothelial cell receptors. This can cause the BBB to move through receptor-mediated transcytosis (89). In vitro studies of swine brain capillary endothelial cells showed that functionalized liposomes could internalize themselves, and in animal models, they could even reach the brain (90). Even though there isn't a lot of information about how well liposomes work for brain infections, these studies showed that they have the power to get through the blood-brain barrier and deliver antimicrobial drugs to the brain, where they can have a bigger effect on treatment(91).

4.2. Bactericidal potency and efficacy improved

One of the most important characteristics of antibiotic-loaded liposomes is their increased antibacterial activity in comparison to the corresponding antibiotic in its free form (92). Numerous studies have reported liposomal antibiotic formulations with increased potency, even against resistant strains (93). Regardless of the added antibiotic, cationic

liposomal formulations often have more antibacterial activity than anionic or neutral formulations (94). Along with their lipid charge, liposomes' fluidity or fusogenic properties also help them interact with bacteria better (95). So, the process of liposome-bacteria fusion is affected by the lipid content and the presence of fusogenic chemicals on the liposomal surface (96). Research demonstrates that the addition of the fusogenic lipid DOPE (dioleoyl phosphatidyl ethanolamine) to a liposomal formulation amplifies its bactericidal action (97). "Fuidosomes," a well-known lipid composition, and the bacterial membrane both play a significant role (98). Consequently, the liposomal formulations broke down one of the most effective impermeable barriers that caused bacterial resistance (99).

Liposomal nanoparticles serve as carriers for the delivery of antibacterial agents (100-102).

- Liposomal nanoparticles larger than 100 nm
- Liposomal nanoparticles smaller than 100 nm

5. Conclusion

Antibiotic administration via liposomes, microscopic lipid bilayer vesicles, has been extensively researched. Liposomes have many benefits for antibiotic delivery. Antibiotics can be encapsulated in liposomes to prevent degradation and increase stability. Controlled release of the antibiotic from this encapsulation may improve treatment efficacy and reduce side effects. Due to their improved permeability and retention, liposomes can passively accumulate in inflamed or infected tissues, targeting specific infection sites. Targeted delivery boosts antibiotic concentration at the infection site, increasing treatment outcomes. Liposomes can also transport hydrophilic and hydrophobic antibiotics, broadening their antibiotic delivery options. In conclusion, liposomes can improve antibiotic efficacy as a medication delivery mechanism. The capacity to prevent, target, and control antibiotic release makes them useful in fighting infections. More research could lead to more effective and targeted antibiotics.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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