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REVIEW

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Liposome drug delivery in combating the widespread topical antibiotic resistance: a narrative review

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Abstract

Background The increasing trend of antibiotic resistance has posed challenges for scientists, especially in developing better drug formulations. The discovery of new antibiotics could take years. Therefore, the management of an ideal drug delivery system has become a primary focus nowadays.

Main body of abstract Almost all skin diseases could be treated with the administration of topical drugs, especially infectious skin diseases. The increasing cases of antimicrobial resistance require innovative strategies and actions. In dermatokinetics, achieving optimal drug concentrations in the deepest layers of skin tissue is a significant challenge. Human skin has remarkably complex characteristics, presenting a major obstacle in efficiently maintaining drug efficacy. Nanocarriers are an important part of nanomedicine which provide excellent drug penetration through various drug delivery systems. Lipid-based nanovesicles, such as liposome, are the oldest and most potential nanovesicles for such a purpose. Several studies have shown the efficacy of liposome-contained antibiotics and offered the lowest microbial inhibition concentration (MIC). It is suggested that liposome also delivers greater drug accumulation compared to blank drugs.

Short conclusion Liposome is a flexible lipid-based drug delivery that enhances drug permeation through skin tissue by mimicking the lipid bilayer system of the organ. It is non-toxic, less immunogenic, and easily degraded by enzyme. The incorporation of liposome into antibiotics may reduce the inefficient drug dosage since the encapsulation will protect the active compounds prior to being released from the vehicle. Thus, the lowest MIC and less clinical side effects will be obtained.

Keywords Antibiotics, Drug delivery, Liposome, Nanomedicine, Topical anti-infective agents

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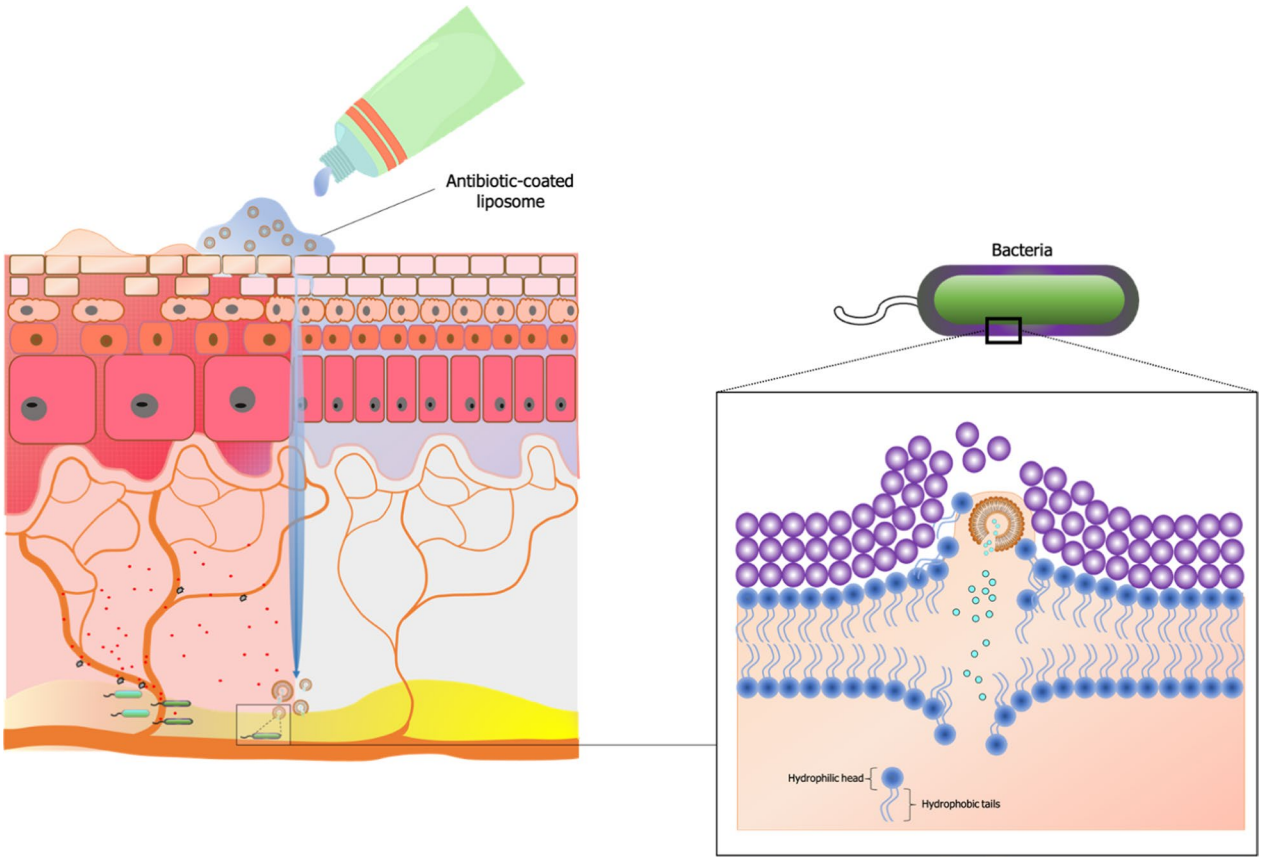
Graphical abstract



1 Background

Most dermatological diseases are commonly treated with topical applications as they can easily reach the target area within the skin tissue compared to other administration routes. However, topical therapies have several disadvantages especially due to improper and irrational use which may lead to detrimental effects, such as emerging cases of antibacterial resistance and incurable complications. There are several well-known topical antibiotics, such as gels, creams, ointments, sprays, and liquids. Most of the topical antibiotics could be purchased over the counter (OTC) without prescriptions since the medical issues are usually mild or do not require medical consultation. A concerted effort is required to prevent more resistance cases in the future. Reports on topical antibiotic resistance are limited compared to those on the systemic route. However, one systematic review has suggested that the cases of antibiotic resistance to *Pseudomonas aeruginosa* (*P. aeruginosa*) have increased drastically. *P. aeruginosa* is known as the main pathogen of acne. The same study reported that antibiotic resistance to *P. aeruginosa* has increased from 20% in 1978 to 62% in 1996. Therefore, some countries, for example, the UK through National Institute for Health and Care Excellence, have released guidelines on antimicrobial stewardship for consultation which help practitioners prescribe and monitor patients' antibiotics [1, 2].

Skin infections are usually caused by the skin flora normal infiltration through open wounds or scars. Most infections are caused by Gram-positive microbes such as *Staphylococcus aureus* (*S. aureus*), *Enterococcus faecalis* (*E. faecalis*), and *Streptococcus viridans* (*S. viridans*). However, Gram-negative bacteria could also cause the infections, for example, *Escherichia coli* (*E. coli*), *Haemophilus influenza* (*H. influenza*), *Clostridium* species, *Mycobacterium* species, *Pseudomonas* species, and other anaerobes [2]. Each type of bacteria could be distinguished by the thickness of its cell wall membrane. Gram-positive bacteria possess

thicker peptidoglycan compared to Gram-negative bacteria with fewer layers. Nevertheless, Gram-negative bacteria are likely to have greater intrinsic resistance against antibiotics, which potentially leads to antimicrobial resistance [3]. While minor infections can be effectively treated with conventional topical antibiotics, recent attention has been directed toward preserving drug efficacy and optimizing bioavailability. Novel drug delivery for topical applications has been an issue not only to limit the widespread of antibiotic resistance, but also to navigate efficient drug molecules to reach targeted tissues. From a dermatokinetics perspective, the fundamental problem of low-level bactericidal activity is usually related to the bioavailability of drug molecules within the tissue. Skin layers have complex structures as they serve as the first anatomical barrier against many pathogens from the environment. Having many variations, the topical route facilitates permeation across the lipid bilayer system of the skin. Conventional topical dermal drug delivery systems (TDDDS) such as ointments, creams, gels, lotions, liniments, and oils are the most popular formulas for treating many skin diseases. However, there is a need for innovative approaches which allow increased drug concentration as the primary limitation of this pathway is the constrained permeability of drug dosages [4, 5]. The pore size and physicochemical properties within an individual's skin type can influence drug accumulation levels. A hydrophilic formulation in a topical drug delivery system provides enhanced capacity for drug molecules to reach specific layers of the skin tissue [6]. Liposome is one of the strategies to improve antibiotics ability to obtain better clinical results in treating skin infections. As reported by Sang et al. [7], liposome can be coupled with ligands or small peptides that can bind bacteria, improving the antibiotic delivery efficiency and avoiding the side effect.

Lipid nanoparticles are a nanotechnology-based advancement in pharmaceutical engineering. Many studies have been conducted to examine their ability to enhance drug delivery to reach specific target within tissues. They can be developed to be sustainable and capable of interacting with proteins in the body. Moreover, when they meet lipid-sensitive enzyme, they can trigger a controlled release mechanism [8]. Nanosized liposome is one of the options to provide the ability but studies focus on the delivery system to encapsulate topical antibiotics are still limited. Thus, this review aims to explain the complexity of skin tissue and dermatokinetics as well as liposome adaptability when it encapsulates various antibiotics to treat skin infections. It also highlights how liposome could enhance topical antibiotics as well as its inhibition ability toward bacteria compared to non-liposome coated. The review also aims to provide insights into pharmaceutical breakthroughs with liposome as a nanocarrier for topical antibiotics. Scoping assessment was conducted to collect data from recorded and ongoing studies within the last ten years (2014–2024).

2 Main text

2.1 The anatomy and physiology of skin

The skin is the widest organ that covers the body. It serves crucial functions as a physical barrier, sensory organ, and immunology interface. It accommodates homeostasis by limiting the loss of water, electrolytes, and heat. It contains Merkel cells as mechanoreceptors and Langerhans cells or dendritic cells serving immune functions [9, 10]. Skin tissue comprises three different layers: the epidermis, dermis, and subcutaneous tissue (Fig. 1). The epidermal layer is composed of squamous epithelium and is stratified based on the level of keratinization exhibited by the cells. The layers include the stratum basale (comprising basal cells) at the base, the stratum spinosum (comprising spinous or prickle cells), the stratum granulosum

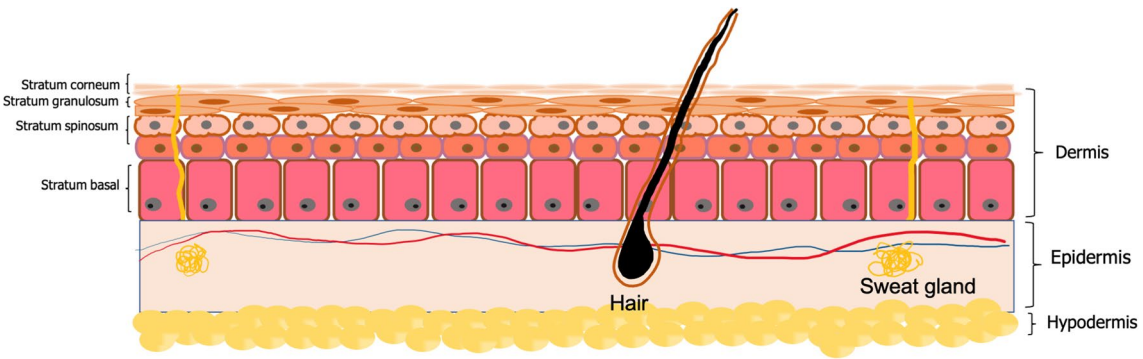


Fig. 1 Skin histology

(comprising granular cells), and the stratum corneum (comprising corneocytes). The stratum corneum (SC) is held together by lipid bilayers organized in a brick-and-mortar configuration [9, 11]. Stratum corneum forms a hydrophobic layer with 10–30 μm thickness and functions as a prominent barrier for skin permeation. In addition to corneocytes, the skin barrier consists of a highly lipidic component comprising keratin filaments and filaggrin. Corneocytes are embedded within multilamellar lipids composed of sterols, phospholipids, and glycosphingolipids [10]. Corneocytes have a rigid structure, lack functionality (are non-viable), do not contain a nucleus, and are rich in keratin [12]. In the stratum corneum, corneocytes show a flat hexagonal shape aligned parallel to the skin surface, characterized by an irregular morphology. They have a diameter of approximately 40 μm, a width reaching up to around 1 μm, and an intercellular lipid area thickness of up to 0.1 μm. The corneocytes and lipids in the stratum corneum have a compact brick-and-mortar-like configuration, serving as a formidable barrier to the permeation and diffusion of substances applied topically or transdermally. This structure functions as a barrier impeding the skin absorption of topical products [13, 14]. In the stratum basale, cells undergo active proliferation and keratinization. They move toward the outer layers, reaching the stratum corneum. The route of skin permeation entails drug passage through the epidermis and associated skin appendages, predominant hair follicles, and sweat glands, which represent an alternative path to the intact epidermis. These skin appendages collectively cover approximately 0.1% of the human skin surface [5, 12].

Dermis is the deeper layer below the epidermis. The thickness of dermis is 3–5 mm, and it consists of fibrous proteins (such as collagen and elastin) and an interfibrillar gel of glycosaminoglycans, salts, and water. It also contains appendages, including sweat gland, pilosebaceous units, blood vessel, and nerves. The dermis supports the binding between epidermis and subcutis, keeping the tensile strength, elasticity, and resilience [10]. It also supports nutrient and oxygen delivery as well as waste removal from epidermis by diffusion across dermo-epidermal junction [15]. Dermis also contains a range of immune cells, including macrophages and dermal dendritic cells. The dermis serves as the pathway for drug permeation through the transcellular route (diffusion across corneocytes), intercellular route (diffusion through the lipid matrix), and the shunt pathway or appendageal route (diffusion into sweat glands, hair follicles, and sebaceous glands) [10].

However, the outer physical barrier contains nonliving components (called "dead") [14]. The subcutaneous layers, the epidermis and dermis, contain living components. The subcutaneous layer has three zones: the basal zone (with thick, dense keratin consisting of 4–10 cells), the intermediate zone (with denser keratin loosely composed of 8–12 cells), and the superficial zone (with less keratin, 2–3 cells). The subcutaneous layer is a dynamic barrier; it can be modulated by topical drug delivery systems, which can make a drug able to penetrate or fail to penetrate the layer. The establishment of the subcutaneous barrier is influenced by dead corneocytes within a flat, water-repellent sheath in an extracellular lipid matrix by the proteolytic breakdown of corneodesmosomes. These cohesive molecular bonds between corneocytes encompass approximately 30% of the overall surface volume of the compact stratum corneum layer [14]. The hypodermis layer comprises loose connective tissue and adipose tissue. The components of dermis and hypodermis are blood vessel, lymphatics, nerve cells, and skin appendages. The surface covered by the appendages is only about 0.1% of the skin continuum [10]. Although the absorption of compound is small, this route enables permeation of charged molecules and large polar compounds, such as peptide-based drugs [12].

2.2 Permeability of the skin

Understanding the skin permeation system is important before formulating a suitable topical drug delivery. Skin is the first barrier which provides strong immunity protection toward various threats from the environment such as biological, mechanical, chemical, and physical attacks [16]. Overall, the width of skin tissue could extend to approximately 2 m^2 and comprises several layers. Each layer has specific functions based on its histological feature. From outward to inward, skin tissue consists of living epidermis, dermis, and hypodermis. Epidermis structure comprises five different layers: stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. Among these layers, the stratum corneum should be considered for topical administration [16, 17]. Prior the permeation process, an important variable that must be considered is the partition phenomenon. In terms of drug pharmacokinetic, partition relates to the distribution of the drug. The partition occurs between the drug vehicles and the surface of the skin tissue to finally achieve the balance during the process; diffusion and partition will repeatedly take place until the whole drug molecules reach the capillary system. Defining the partition potency requires an absolute value which explains the ratio between the two involved variables. Partition coefficient (K) helps to determine the strategy to increase drug absorption through skin barrier especially if the drug is designed as a transdermal route [18, 19]. Based on the definition, K is a value used to estimate the drug concentration of a certain skin drug route

toward its delivery system [20]. To achieve the coefficient, studies to retrieve the information have been conducted. In a study using human viable epidermis and stratum corneum layers, the partition coefficient was obtained by measuring the concentration of drug compound in the tissue or lipid (per gram of tissue or lipid weight) and the concentration of drug compound in the buffer at equilibrium (24 or 2 h). In another study, the partition coefficient was defined as the mass of chemical per unit mass of dry stratum corneum relative to the mass of chemical in buffer per volume of buffer. The study revealed that K value was higher in lipidized sample than that in the delipidized stratum corneum (fully hydrated). The size of compound, less than 500 Da, is easily penetrates through passive diffusion across lipid bilayer of cell membrane and further passes the absorption step [21]. Aside of partition coefficient, another important parameter needed to observe and analyze skin penetration ability is diffusion coefficient (D). Diffusion coefficient is obtained by measuring the steady flux values and its lag time. However, only a limited number of studies have documented the diffusion coefficient of the skin due to limitations of models and methodologies. Both parameters could be employed to calculate the skin's absorption rate [22].

The stratum corneum of the skin serves as the main location for percutaneous drug absorption since it consists of corneocytes and is enriched with intercellular lipids. Thus, it has an hydrophobic ability. The corneocytes are connected through desmosome to ensure the strength of tissue connectivity and permeability for most hydrophilic molecules greater than 200–350 Da [6]. The intercellular lipids form a matrix which contains stratified hydrophilic and hydrophobic layers arranged into thick layers as multilamellar sheets [16, 18, 23]. Due to the rich staggered corneocytes available in stratum corneum, the opportunity for lipoidal diffusion to occur is high. It is approximately 1000 times more hydrophobic [16]. The stratum corneum plays a crucial role in moisturizing the outermost skin layer. Excessive loss of overall body water may result in dry skin, affecting the drug's ability to permeate effectively. Various known routes for drug molecule to access systematic circulation are intracellular, intercellular, and transfollicular routes [6]. However, the basic mechanism of permeation system usually depends on the physiochemical property of the drug molecules. Highly hydrophobic drugs are difficult to permeate through the hydrophilic layer and vice versa [6, 24]. The difference between the available routes is mostly related to the size and lipid solubility of penetrated molecules. Hydrophilic compounds most likely penetrate through the crevices found inside the lipid layer surrounding the corneocytes. Intercellular pathway allows for hydrophilic molecules to pass the lipid matrix. Yet, it requires exact sequential diffusion and partitioning amid the alkyl chain length and the polar head groups of intercellular lipids [6, 16, 25]. The intracellular pathway initiates diffusion that allows the molecules to run deeply into the keratin [16]. Lower pKa value on the skin surface also allows for better permeation if the drug compound is bound under acidic vehicle due to the higher unionized level on the skin surface. If the partition coefficient is known, then further calculation to measure flow rate of skin permeation of certain drug molecules could be obtained through Fick's second law [18].

2.3 Dermatokinetics of applied topical drugs

After a topical preparation is applied to the skin, the drug must be able to penetrate deeper layers by crossing the various layers [13]. Therefore, only a small drug concentration can penetrate the skin layers within a certain period [26]. The dermatokinetics concept emphasizes three mechanisms: (1) The stratum corneum layer limits the rate of drug absorption; (2) the drug diffusion process affects the drug concentration penetrating the dermis layer; the concentration is equal to the drug concentration in the stratum corneum; and (3) the drug concentration in the skin layers (stratum corneum, epidermis, dermis) describes the dermatological effectiveness of the drug [13]. The delivery of drugs to the skin involves several processes: (a) drug release from the dosage form; (b) drug penetration through the stratum corneum; (c) drug diffusion across the stratum corneum, primarily via intercellular lipids; (d) drug separation from the stratum corneum into the viable epidermal layer; (e) drug diffusion through the epidermal layer to the underlying dermis; and (f) drug absorption by capillaries, leading to systemic circulation [12].

Water component is essential in most topical drug delivery systems because it quickly penetrates the surface layer. Water can cause the subcutaneous layer to soften and thicken (toward the surface and not laterally), reduce the depth of the groove, and reduce subcutaneous corneocyte undulations. Topical formulations alter subcutaneous hydration by modulating water content in the stratum disjunctum, with slight changes in water content in the stratum compactum. The insoluble and protective corneocyte sheath is also affected by stratum corneum hydration, which influences protease activity. The sheath is irregular, deformed, and brittle in its underlying layers, but 80% of superficial subcutaneous corneocytes are polygonal and very strong. This decrease in subcutaneous corneocyte maturation can be influenced by environmental exposure or skin dryness, which can reduce the resistance of the sheath. The impact of heterogeneous skin morphology determines how quickly the drug can penetrate layers layer of the

skin and be effective for topical treatment. Drugs will pass through the subcutaneous layer more easily if they contain additional formulations in the form of one or more chemicals to increase their penetration ability, have a small molecular weight (≤ 500 Da), have high solubility, and are sufficiently lipophilic (logarithm of octanol partition candidate—water coefficient log *P* in the range 0–5). However, those with a larger molecular weight are more lipophilic and more difficult to pass through epidermis due to their poor solubility in water [14, 27].

Transportation of drugs in and out of the subcutaneous lipid layer by permeation along the corneocytes mainly occurs via the lipid pathway only. The thickness of the subcutaneous extracellular lipid layer varies and depends on the number of lipid bilayer layers at any given cross section. Each bilayer illustrated is approximately ~ 11 nm wide and consists of narrow segments (~ 4.5 nm) and broad segments (~ 6.5 nm) arranged in alternating parallels [12, 28]. The thick lipid region extends 41 mm between subcutaneous corneocytes, while the thinnest interface is ~ 250 nm long [14, 29]. Other structures that can be a barrier to drug entry into the subcutaneous extracellular lipid space are the densely packed junctions and corneodesmosomes that appear in the stratum corneum's lowest cell layers and the stratum granulosum [27–29].

Biopsy results showed > 100 lipid bilayers in one location. Corneodesmosomes are distributed in various body locations and can be influenced by previous treatments or disease. Corneodesmosomes are commonly found on corneocytes' inner and outer subcutaneous surfaces in winter-induced xerotic skin, outer palmoplantar, xerotic, ichthyotic, and soap-induced hyperkeratotic skin [26, 29]. Hyperkeratosis can also be caused by genetic mutations that affect corneodesmosome proteolysis, such as in psoriasis patients. Thus, if corneodesmosome degradation continues, it will increase subcutaneous thickness. This does not mean that thicker subcutaneous tissue is less permeable. However, water and other solutes can have a tenfold higher permeability through the 400- to 600-μm-thick plantar subcutaneous compared to the thinner abdominal subcutaneous (20–30 μm), with a subcutaneous diffusion coefficient difference of up to 150 times. Because it has a thicker layer, the time lag for solutes passing through the plantar skin maybe ten times longer than the abdominal skin. Therefore, drug transport through subcutaneous lipids varies and is influenced by the location, be it the depth or location of the subcutaneous (at the edge of the corneocyte or on the surface of the corneocyte) and environmental influences, as well as skin diseases associated with corneodesmosomes [5, 26, 29].

When initially applied, the drugs will pass through hair follicles [5]. Drug absorption into the skin is influenced by several factors, such as molecular size, lipophilicity, formulation pH, penetrant concentration, chemical additives, skin hydration, and skin enzymes. The absorption ability of a drug is inversely proportional to its molecular weight and mainly affects the diffusion coefficient. Molecules larger than 500 Da will have more difficulties in penetrating the subcutaneous tissue. The permeability of drug molecules will be optimal at a lipid/water partition coefficient of 1 or greater. Drug formulations with excessively high or low pH levels can potentially damage or irritate the skin. Therefore, a neutral pH value (typically above the skin's isoelectric point, pH 4) may be more appropriate for topical application. The degree of drug ionization at a certain pH will affect its ability to diffuse through the lipophilic intercellular areas in the subcutaneous layer and form pairs with ions in the skin to produce neutral compounds to cross the skin barrier. Drug delivery through the skin can avoid the first-pass effect in the liver, the physiological environment, and chemical or metabolic degradation in the gastrointestinal tract, such as changes in pH and luminal microflora. In addition, the slow plasma concentration of topical medications can reduce the side effects. Absorption of the drug into the skin occurs more slowly through passive diffusion. The speed of drug delivery across the stratum corneum depends on the solubility of the drug in water, the oil/water partition coefficient, the drug concentration in the formulation vehicle, the size and shape of the molecule, the surface area of the skin to be exposed, and the thickness of the stratum corneum [26].

Complete penetration ability can be achieved if all parameters are stable. Key parameters crucial for determining the efficacy of topical medication consist of C_{max} (maximum drug concentration in the skin layers), T_{max} (time required to reach C_{max}), and AUC (area under the curve) in all skin layers. However, these parameters could only be observed through in vitro or in vivo experiments. Various methods have been employed in previous studies to assess topical products and their dermatokinetic profile such as tape stripping, microdialysis and open-flow microperfusion, vasoconstrictor assay, and microscopic and spectroscopic methods [13]. Tape stripping is simpler compared to other methods as it relies solely on the adhesive quality of applicators. However, various factors may introduce bias, such as skin conditions like scar tissue, pH, TEWL (transepidermal water loss), hydration, sebum content, and adhesion with the stratum corneum cells. This method is more effective when the study specifically aims to observe barrier restoration following adhesion [30]. To develop clinically effective

topical products, it is essential that they demonstrate substantial skin bioequivalence (BE). Some studies have shown that pharmacokinetic endpoints should typically fall within specified BE limits (usually 0.80–1.25) on a log transformed basis (95% CI). Dermal open-flow microperfusion (dOFM) enables the assessment of intradermal biochemistry and drug concentrations by sampling dermal interstitial fluid for up to 48 h. This method of dermatokinetics assessment enhances monitoring, particularly for lipophilic drugs and larger proteins, using an inserted probe into the intradermal region. The area surrounding the probes is then scanned with longitudinal ultrasound to evaluate drug accumulation [31].

2.4 Various drug delivery strategies for topical route

Topical drugs are the safest option with minimal side effects and are primarily used to treat skin conditions. Their ease of application and high drug concentration make them a popular choice for long-term treatment [32]. The anatomical and physiological barriers in the skin pose challenges for effective penetration by foreign substances which affect the development of topical drugs. Topical drug delivery forms include solid (powder, plaster, ointments), semi-solid (gels, creams, ointments), liquid (lotions, solutions, emulsions, suspensions), and miscellaneous (patches, topical aerosols, rubbing alcohols, liquid cleansers) [33].

Topical delivery systems can target skin melanocytes for whitening, act as anesthetics for pain relief, serve as anti-infective agents, and activate Langerhans cells. The appropriate topical agent or delivery system is crucial, with consideration given to the specific skin cell type being targeted [34, 35]. The earliest method for improving skin absorption is by choosing the appropriate drug. Essential techniques such as selecting raw materials, utilizing eutectic systems, employing ion pairing, and understanding chemical potential are necessary for producing high-quality products. Topical drug absorption is primarily influenced by two factors: physiological aspects (such as skin thickness, pH, and type) and physicochemical properties including molecular weight and ionization [35]. Gels and creams are topical medications commonly available. It is essential to optimize the drug vehicle, particularly for topical applications. However, not all traditional topical forms can effectively incorporate active drug ingredients, such as antibiotics. Creating a conjugation or network system by combining materials is often challenging and may take years to develop the ideal formula. One strategy commonly used by many researchers is utilizing existing drug delivery components with more efficient release systems, such as lipid-based drug delivery. In addition to lipids, non-organic materials like gold and silver have also been found to be easily adaptable for use as drug delivery systems [36]. A study has shown that blank cationic liposomes combined with carboxyl-modified gold nanoparticles (AuC) efficiently penetrated *S. aureus*, with fluorescence microscopy indicating higher activity at lower pH levels (pH 4.5). This suggests the formulation could enhance antimicrobial efficacy within bacteria upon liposome loading [37].

Nanotechnology is a vital breakthrough in various fields, particularly pharmaceuticals. However, many traditional topical drug delivery systems still rely on larger materials. Skin permeability becomes the first obstacle to overcome before achieving clinical efficacy. The utilization of large materials in drug delivery presents significant challenges, such as in vivo instability, limited bioavailability, poor solubility, inadequate absorption, target-specific delivery issues, diminished effectiveness, and potential adverse drug effects [38]. The use of topical antibiotics is the main and important component in the treatment of skin infections. Several skin infections such as dermatitis, acne, and impetigo require antimicrobial agents that are easy to use without side effects. Generally, topical antibiotics work by suppressing bacterial growth and changing the condition of the skin so that they can support the repair of skin cells. This will help heal from infections. The antibiotics mupirocin, neomycin, and aminoglycosides have a broad spectrum so they are often recommended for the use of topical antibiotics. Irrational use of topical antibiotic may cause more harm than benefits. Despite the growing number of challenges, especially antibiotic resistance, various nanoplatforms have been introduced, studied, and modified alongside the current drugs. The primary aim is to achieve optimal formulas for specific drug delivery to effectively target and retain drug molecules within the intended tissues. Over the years, nanotechnology has led to significant advancements in medicine, particularly in the field of nanomedicine. The first generation of nanoparticle-based therapies included lipid systems like liposomes and micelles, which are now (Food and Drug Administration) FDA-approved for medical use [39].

Nanotechnology-based formulations, especially nanoparticle formulations, have many types and forms. For decades, researchers have tried to create adjustable drug delivery methods for skin diseases. However, the strong barrier in skin tissue limits the range of available strategies. Solutions have been explored, ranging from active methods like microneedles, electrophoresis, and sonophoresis to passive approaches such as carrier-mediated delivery involving chemical permeation enhancers and nanovesicular carriers [40–42]. Nanovesicles are typically classified based on their lipid solubility into phospholipid and non-phospholipid types. Various types of nanovesicles include ethosomes, liposomes, glycerosomes,

transethosomes, bilosomes, polymersomes, exosomes, transfersomes, phytosomes, and niosomes. Numerous studies indicate the use of nanovesicles to enhance skin permeability, particularly in hydrogel form. When designing specific nanovesicles, it is crucial to evaluate and adjust key parameters such as size, composition, drug diffusion into skin layers, surface charge, and deformability. It is important to determine the size of nanovesicles. Nanovesicles over 600 nm may not penetrate deeper layers of the skin, particularly the subcutaneous layer. Smaller sizes (< 300 nm) are preferred as they can potentially penetrate even deeper into the dermal region. Nanovesicles loaded with various drugs are widely reported to effectively treat skin diseases, as summarized in Table 1.

The natural characteristics of liposome enable encapsulation of both hydrophilic and lipophilic substances/drugs. Some liposome-based nanovesicles products have been approved by FDA and commercialized for medicinal purpose since they are non-toxic and effective. Liposomal-based transdermal drug has commonly been used, foe examples diclofenac, ketoprofen, and azithromycin [6]. Another phospholipid-based nanovesicle is the ethosome, composed mainly of phospholipids mixed with alcohol (20–40%, such as ethanol). Ethanol enhances the penetration flexibility of the ethosome. This nanocarrier boasts enhanced drug loading capacity and deformability, making it superior to liposomes. Modified versions like transethosomes include phospholipids, higher ethanol content, and surfactants. The increased ethanol concentration in transethosomes enhances permeation, which makes them a viable alternative for transdermal drug delivery for treating various skin conditions. Ethosomes, a lipid delivery system, have shown improved efficiency in percutaneous drug delivery due to their rounded shape that accumulates greater deposits in deeper skin layers [34]. Transdermal drugs using liposomal have been used to load a range of oral medications, including antihypertensive agents like valsartan, along with antifungal treatments like econazole nitrate and mitoxantrone. Transfersomes consist of a lipid bilayer incorporating phospholipids, ethanol, and an aqueous component. Typically, surfactants are added to optimize consistency. The distinct structure of transfersomes enables deep skin penetration [33]. Niosomes are non-ionic surfactants which are thermodynamically stable. They are commonly used for controlling and targeting drug delivery due to their sustained release. Typically ranging from 10 to 1000 nm in size, they offer enhanced skin layer penetration compared to liposomes [34, 73].

There are several methods for preparing nanovesicles before loading them with active compounds. The common methods for liposomes include the thin-film method and injection methods (similar to the ethanol and ether methods). Among these, the thin-film method is the most popular. In this technique, a thin lipid film forms on the inner wall of a rotary evaporator flask, which is then hydrated with a water or buffer solution. Subsequent vigorous shaking and sonication in an ultrasonic bath help the film detach from the flask and form liposomes. The objective of injection method is to ensure that the lipid suspension (for either hydrophobic or hydrophilic organic solvents) is injected into the water. For example, in ethanol injection, the first step is preparing liposomes ranging between 30 and 170 nm. When preparing liposomes using this method, the lipids dissolved in an organic solvent (in this case ethanol) are injected into the water for stirring, and then, the solvent is removed, followed by hydrating the solution during stirring for another 15 min. Ethanol can be removed from the liposome suspension through either rotary evaporation or centrifugation with a silica gel column. The ether injection method, resembling ethanol injection, enhances lipid solubility and ensures robust liposome stability since the solution does not dissolve in water. Unlike the injection method, emulsification forms the organic phase. This technique offers potentially higher encapsulation efficiencies compared to injection methods [74].

The cold method is the most commonly used approach for ethosome preparation. Phospholipids, drugs, and other lipid materials are dissolved in ethanol within a covered vessel at room temperature under vigorous stirring. The mixture is heated to 30 °C in a water bath. Water in a separate vessel is also heated to 30 °C and then added to the mixture, then stirred for five minutes in a covered vessel. Sonication or extrusion can be utilized to adjust the vesicle size of the ethosomes formulation. Finally, the formulation must be properly stored in a refrigerator. In the hot method, drugs are initially dissolved in a mixture of ethanol and propylene glycol. This mixture is then added to the phospholipid dispersion in water at 40 °C. After a five-minute mix, the preparation undergoes sonication at 4 °C for three cycles of five minutes each, with a five-minute break between each cycle, using the Probe Sonicator. The formulation is homogenized at 15,000 psi pressure in three cycles using a high-pressure homogenizer to obtain nanosized ethosomes. In the Classic Mechanical Dispersion Method, organic ingredients like Soya phosphatidylcholine are combined and dissolved in a mixture of chloroform to methanol (3:1 ratio) in a round-bottom flask. Removing the organic solvents using a rotary vacuum evaporator above the lipid transition temperature forms a thin lipid film on the flask's wall. Remaining solvent traces are eliminated by vacuum exposure overnight. Hydration involves different concentrations of a hydroethanolic mixture containing

Table 1 Summary of studies related to nanovesicles application for various skin infectious diseases

Type	Preparation	Active compound(s)	Disease	Model of study(s)	Results	References
Liposome	Thin-film hydration method	Eberconazole Nitrate	Fungal skin infection	Ex vivo skin retention study (Franz diffusion cell): goat skin	Liposome-loaded Eberconazole Nitrate has 77.55% drug release compared to conventional gel (29.35%)	[43]
Liposome	Thin-film hydration method	Ketoconazole	Fungal skin infection	In vitro: *Candida albicans*	Ketoconazole-loaded liposome showed inhibition zone 39 mm with MIC 67 µg/mL	[44]
Liposome	Thin-film hydration method	Griseofulvin	Superficial fungal infections	In vitro antifungal effect: *Microsporum gypseum* and *Epidermophyton floccosum*	Inhibition zone ± SD of liposome containing Griseofulvin is 18 ± 0.82 mm (*Microsporum gypseum*), 18.75 ± 0.5 mm (*Epidermophyton floccosum*). 2.5 times higher than control group	[45]
Liposome	Emulsion method	Terbinafine	Superficial fungal infections	In vitro releasing test: Franz cell diffusion Ex vivo permeation study: pig's ear skin	1% liposome cream containing terbinafine (TH Liposome) reached 57 µg/cm^2 in less than 40 h. Meanwhile, ex vivo study suggested concentration of TH Liposome reached 104.75 µg in stratum corneum and viable epidermis	[46]
Liposomes-in-Hydrogel	Thin-film hydration method	Azithromycin	MRSA-related skin infection	In vitro: *S. aureus* (ATCC 29213) and five clinical isolates of MRSA (Methicillin-resistant *S. aureus*) strains	In all MRSA isolates, the Azithromycin-loaded liposomes were 32 times more effective at inhibiting biofilm formation than free Azithromycin	[47]
Liposome	Dry film dispersion method	Daptomycin	Skin infection	In vitro: *S. aureus* In vivo: rats' dorsal skin	Scanning Electron Microscopy suggested massive damage of *S. aureus* biofilm in liposome-loaded Daptomycin group after 2 h observation, the drug distribution in dermis and subcutaneous layer reached 194.55 ± 12.48 µg/g (4.86% of total dose) and 175.30 ± 11.54 µg/g	[48]
Liposome	Thin-film hydration method	Vancomycin	Skin wound infection	In vivo: mice	Isolation of mice' liver, spleen, and blood showed nearly 50% decrease of the colony-forming units (CFU) (295 ± 22 CFU/g to 105 ± 19 CFU/g)	[49]

Table 1 (continued)

Type	Preparation	Active compound(s)	Disease	Model of study(s)	Results	References
Liposomes-in-Hydrogel	Dry film method	Mupirocin	Burn wound infection	In vivo: mice with burn wound model (~ 1 cm in diameter)	Mupirocin-in-liposomes-in-chitosan showing significantly ($P < 0.05$) faster healing compared to the other group	[50]
Hydrogel-in-Liposomes	Thin-film hydration method	Berberine hydrochloride	Burn wound infection	In vivo: full-layer skin resection model in mice	Quantification with ImageJ Software all groups of liposome-loaded Berberine hydrochloride had the lowest wound shrinkage (post 13 days of observation)	[51]
Liposome	Solvent-injection method	Rifampicin	Superficial skin and soft tissue infection	In vitro: MRSA	The liposome-loaded-rifampicin embedded with dissolving microneedles showed approximately 45 mm inhibition zone compared to blank dissolving microneedles (< 20 mm)	[52]
Liposome	Thin-film hydration method	Amphotericin B, Imiquimod, and Indole	Cutaneous Leishmaniasis (CL)	In vivo retention study: BalbC mice	Fluorescence appearance showed liposomes penetrate until 15 microns through clusters and 30 microns through canyons of corneocytes. However, no significant differences between each formulation were found	[53]
Liposome	Film formation method	Tetracycline HCl and tretinoin	Acne vulgaris	In vitro: *S. aureus* ATCC 29213 and *S. epidermidis* ATCC 35984	MIC values for liposomes containing tetracycline and tretinoin 0.016 µg/mL (12.8-fold reduction in MIC values)	[54]
Liposome	Thin-film technique	Proteinase K (PK), retinoic acid (RA), and soyethyl morpholinium ethosulfate (SME)	Acne vulgaris	In vitro: *Cutibacterium acne*	MIC liposomes (NV/SME and NV/PK/SME) 0.49 µg/mL (2—fourfold reduction)	[55]
Liposome	Thin-film hydration method	Third-generation retinoid (Adapalene)	Acne vulgaris	In vivo: mice with testosterone-induced acne model	The mice in treatment group (liposome containing adapalene) had no visible acne lesions but obscene inflammation	[56]
Liposome	Thin-film hydration method	Third-generation retinoid (Adapalene)	Acne vulgaris	Ex vivo skin retention study (Franz diffusion cell): goat skin	Spectrophotometric evaluation: ± 89.24% of drug (Liposomal encapsulation of adapalene) was accumulated in dermis and epidermis layer	[57]

Table 1 (continued)

Type	Preparation	Active compound(s)	Disease	Model of study(s)	Results	References
Liposome	Modified ethanol injection method	Rhodomyrtone	Acne vulgaris	In vitro: *S. aureus*, *Staphylococcus epidermidis* (*S. epidermidis*), *Propionibacterium acnes* (*P. acnes*)	MIC liposomes containing Rhodomyrtone 0,25 µg/mL (*P. acnes*), 0,25–1 µg/mL (different isolates of *S. aureus*), 0,25–0,5 µg/mL (different isolates of *S. epidermidis*)	[58]
Liposome	Modified ether injecting method	Tretinoin	Acne vulgaris	Clinical study: 12 Egyptian patients aged > 18 years with acne vulgaris (papules, closed comedones, and open comedones) on their face	Formula 13 composed of [(0.025% tretinoin, phospholipid– cholesterol–dicetyl phosphate, 9–1–0.01) and prepared by film hydration method] and incorporated into 1% carbopol gel showed a significantly ($p < 0.05$) superior efficacy compared to the marketed product over a 4-week period	[59]
Liposome	Lipid film hydration method	Azelaic acid	Acne vulgaris	In vitro: *S. aureus* ATCC 25923, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *P. aeruginosa ATCC 27853*	Inhibition zone ± SD (standard deviation) of liposome containing azelaic acid 20% is 26 ± 0,20 mm (*S. aureus*), 24 ± 0,13 mm (*E. faecalis*), 19 ± 0,14 mm (*E. coli*), 10 ± 0,20 mm (*P. aeruginosa*)	[60]
Liposome	Film hydration method	Curcumin extract	Acne vulgaris	In vitro: *P. acnes* ATCC 6919 (macrolide sensitive) In vivo: ear skin of Sprague Dawley rats	Inhibition zone ± SD of liposomal gel containing curcumin extract is 13,1 ± 1,4 mm Combination therapy of co-application of curcumin and lauric acid liposomal gels: reduction of both concentration of TNF-α and IL-1β with ~ 2.5 and ~ 1.9 fold	[61]
Ethosome	Cold method	*Zingiber zerumbet* Linn extract	Skin fungal infection	In vitro: *Candida albicans*	The MIC of ethosomes loaded with *Z. zerumbet* Linn rhizome extract was 312.5 µg/mL, which is five times higher than that of *Z. zerumbet* Linn rhizome extract	[62]
Binary- Ethosome	Cold method	Ketoconazole	Skin fungal infection	In vitro: *Candida albicans*	Inhibition zone of all groups with binary ethosome-loaded (at concentration 212.5 to 850 µg/mL) is 10 ± 1 to 24 ± 1 mm	[63]

Table 1 (continued)

Type	Preparation	Active compound(s)	Disease	Model of study(s)	Results	References
Ethosome	Ethanol injection method	Farnesol	Cutaneous candidiasis	In vitro: *Candida albicans*	Cell viability rate decreased to 43% for farnesol-ethosomes group	[64]
Ethosome	Cold method	Ashitaba leaf extract	Burn wound infection	In vivo: mice with burn wound model	Wound healing is faster in group ethosome-loaded extract especially the T3 group (2,5% extract concentration) with re-epithelialization area reach 2,8 ± 0,45 cm	[65]
Ethosome	Cold method	Cryptotanshinone (CPT)	Acne vulgaris	In vivo: rabbits' ear skin	The skin recovered normal structure after treatment with CPT-loaded ethosomal gel. There was no inflammation in the pilosebaceous unit and no keratoplasia in the pilosebaceous orifice and SC	[66]
Ethosome	Hot method	Isotretinoin	Acne vulgaris	In vitro permeation study: Franz diffusion cell	The amount of drug deposited was 15-folds higher in ethosomal gel	[67]
Niosome	Thin-film hydration technique	Artemether	Cutaneous leishmaniasis	In vitro: *Leishmania major*	Cell viability or Artemether-loaded liposome is 10%	[68]
Niosome	Thin-film hydration technique	Melittin	Skin and soft tissue infections	In vitro: *S. aureus* ATCC 25923, MRSA ATCC 43300, *Vancomycin-intermediate S. aureus* (VISA)-87	Mel-loaded NISVs (non-ionic surfactant vesicle) efficiently inhibited the growth of bacteria, particularly MRSA and VISA-87 (6,25 µg/mL)	[69]
Niosomal gel	Ether injection method	Cefoperazone Sodium	Skin and soft tissue infections	Ex vivo diffusion study: abdominal skin or albino Wistar rats	The niosomal gel had a 3.28 times higher flux value than the non-niosomal gel of cefoperazone sodium	[70]
Niosomal gel	Thin-film hydration technique	Itraconazole	Skin fungal infection	In vitro diffusion: Franz diffusion cell	Niosomal gel gave drug release 98.87 while the plain gel was found to be 78.59	[71]
Niosomal gel	Ethanol injection method	Third-generation retinoid (Adapalene)	Acne vulgaris	In vivo permeation study: abdominal rats' skin	Niosomal gel-loaded Adapalene showed significant penetration area about 2.10-fold compared commercialized product (Adaferin® gel ($P \leq 0.0.01$)	[72]

the drug, with the flask rotated at a suitable temperature. The classic method dissolves phospholipids and drugs in ethanol, heating to 30 °C in a water bath, followed by slow addition of double distilled water while stirring at a constant 700 rpm in a closed vessel. Further homogenization involves passing the mixture through a polycarbonate membrane using a hand extruder in three cycles [75].

2.5 Liposome as strategy to increase skin permeability for topical antibiotics

2.5.1 Definition of liposome

In 1961, Alec Bangham first created liposomes and its invention has revolutionized the pharmaceutical field. The application of liposome is now established in various areas such as drug, biomolecules, and gene delivery. Liposomes are spherical vesicles consisting of a lipid bilayer encapsulating an aqueous core. They typically contain phospholipids or synthetic amphiphiles along with sterols like cholesterol to influence membrane permeability. With hydrophilic heads and hydrophobic tails, liposomes can vary in size, composition, charge, and lamellarity. They have emerged as a favored nanocarrier for numerous biomedical uses. The advancements in liposome technology have led to various liposome-based drug formulations for human use, with many products undergoing clinical trials. In 1974, Allison and Gregoriadis noted that liposomes were the first system known to provide adjuvant action due to their identified immunological role and properties. Specifically, negatively charged liposomes containing dicetyl phosphate were found to enhance immune responses against diphtheria toxoid. Liposomes are used as adjuvants in two vaccine systems: Inflexal and Epaxal. The first successful achievement in liposome-based products was the introduction of Doxil® to the US market in 1995 for the treatment of patients with ovarian cancer and AIDS-related Kaposi's sarcoma after the failure of prior systemic chemotherapy or intolerance to such therapy. Gabizon and Barenholz initiated the development of Doxil® in Israel and the USA. It was the first nanosized liposomal product to obtain regulatory approval [76–79]. In transdermal drug delivery, liposomes have a limitation: they often adhere to the inner walls of skin cells, leading to the breakdown of phospholipid bonds and premature leakage of the encapsulated drug before reaching deep skin layers [78]. There are four main types of liposomal delivery systems: conventional liposomes, sterically-stabilized liposomes, ligand-targeted liposomes, and combinations of these. Conventional liposomes are made up of a lipid bilayer containing cationic, anionic, or neutral (phospho) lipids and cholesterol, enclosing an aqueous volume. Its formulations reduced the toxicity of compounds in vivo, through modifying pharmacokinetics and biodistribution to enhance drug delivery to diseased tissue in comparison to free drug. However, the delivery system was prone to rapid elimination from the bloodstream, therefore limiting its therapeutic efficacy. Sterically-stabilized liposomes were made to improve liposome stability and enhance their circulation times in the blood. The hydrophilic polymer, polyethylene glycol (PEG), has been shown to be the optimal choice for obtaining sterically-stabilized liposomes. This not only reduces the elimination of drugs by prolonging blood circulation and providing accumulation at pathological sites, but also attenuates side effects. Steric stabilization strongly influences the pharmacokinetics of liposomes, with reported half-lives varying from 2 to 24 h in rodents (mice and rats) and as high as 45 h in humans, depending on the particle size and the characteristics of the coating polymer. Ligand-targeted liposomes offer a vast potential for site specific delivery of drugs to designated cell types or organs in vivo, which selectively express or over-express specific ligands (e.g., receptors or cell adhesion molecules) at the site of disease. Many types of ligands are available, such as antibodies, peptides/proteins, and carbohydrates. The coupling of antibodies, particularly monoclonal antibodies, to create immunoliposomes represents one of the more versatile ligands that can be affixed to liposome surfaces [80, 81]. Improved traditional liposome compositions achieve the deeper permeation of active ingredients to different skin strata. Liposomes of ultraflexible vesicles are common vectors in transdermal drug delivery systems that are relatively liquid and deformed. It demonstrates improving skin penetration and many clinical trials were registered and some of them has been authorized as topically applied medicinal products such as Pevaryl® Lipogel, Maxilene® cream, Lipoxysan®, Supra-vir® cream [82, 83].

2.5.2 Physiochemical characters of liposome

As lipid-based delivery drug, the basic component contained in liposome is amphipathic phospholipid molecules arranged as bilayers with two distinct features on the surface and considered to share similar characteristics with biological membranes. Lipids and fatty acids are joined together to form the primary physical body of liposome (Fig. 2A). The hydrophobic part will be directed into the inner side of the molecule, while the hydrophilic part facing to the outside with both parts is attached spontaneously [84–86]. Surfactant is often added to multiply the liposome's stability and elasticity. Under hydrated environment, each component of liposome is self-assembly and manifests a physical shell of hydrophobic acyl chain. Therefore, it is thermodynamically stable and could be enhanced through various interactions, such as hydrogen bonds, van der Waals

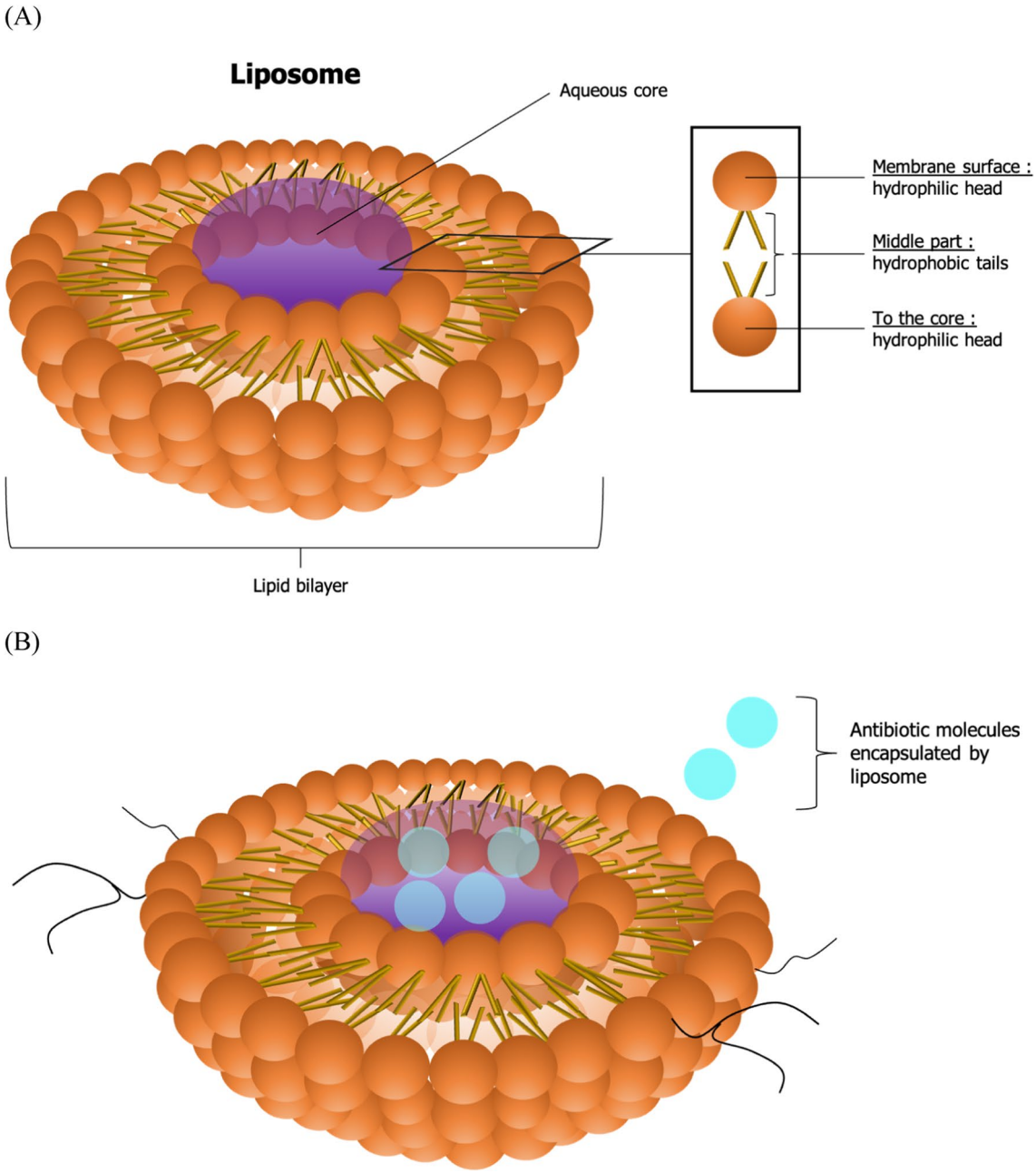


Fig. 2 Liposome is lipid bilayer with an internal aqueous cavity. The lipid bilayer system (**A**) is similar to human tissue membrane that has hydrophilic heads with a hydrophilic area in the middle. The nucleus part of the liposome (**B**) consists of aqueous area that is important for most hydrophilic drug molecules to be kept inside the core

forces, or other electrostatic interactions [87, 88]. The hydrophilic surface is highly polar by nature thus it easily attracts water molecules. The water-resistant surface is owned by the hydrophobic surface, and it is characterized as non-polar sites. Due to its physiochemical nature, liposome could trap both hydrophobic and hydrophilic compounds effectively [85, 89]. In general, liposome could be designed from either natural or synthetic lipids [87].

The utility of liposome as drug carriers has been well known for recent years. Enormous active compounds are trialed to examine liposome's ability in encapsulating them. Various reported studies priorly have claimed the enhancement capacity of drugs molecule to reach

targeted cells after bursting out from the liposome complex molecules. The difference polarities owned by liposome allow interaction with several substances, mostly drug molecules, such as antibiotics, antifungal, anti-virus, and genes. Better bioavailability is considered to improve such wanted therapeutic effects. However, enzymatic destruction often challenges the drug molecule's quality and quantity inside the tissue or cell. The administration route will also affect since many proteins could degrade the liposome early. Even in systematic delivery, reticuloendothelial system (RES) responds to the molecules and metabolizes them instantly. The poor design and characterization are also responsible to the problem. Then, strategies are required to against the issues [86, 90, 91].

To produce high-quality liposome, it is necessary to rely on two basic matters, its size and membrane lamellarity [86]. Liposome is determined based on the synthesis process, the unilamellar vesicle with one bilayer membrane, oligolamellar vesicle with 2–5 bilayer membranes, and multilamellar vesicles with five or more bilayer membranes. The distinguished features among the three types of liposome preparations are seen through the entrapping procedure. The unilamellar vesicle needs to be trapped within a single internal aqueous compartment, while the multilamellar liposome requires some lipid combinations and organic solvent such as cholesterol glycerol, or egg lecithin and mixed with chloroform and methanol as the solvents [34, 92].

2.5.3 Nanoencapsulation method of liposome as nanocarrier

Liposomes are well-investigated nanocarriers for targeted drug delivery. They have improved therapies by stabilizing therapeutic compounds, overcoming obstacles to cellular and tissue uptake, and improving biodistribution of compounds to target sites in vivo. The large aqueous center and biocompatible lipid exterior permit the delivery of a variety of macromolecules, such as DNA, proteins, and imaging agents [80, 93].

Liposomes function as a drug delivery system, penetrating the SC as whole vesicles. This allows them to localize drugs within the SC and the viable epidermis, aiming to reduce systemic absorption and thereby minimize side effects. Besides, the advantages are suitable biocompatibility, low toxicity, and similarity to skin component. Enhancement of the liposomes ability to penetrate the epidermis and dermis layers is conducted by developing new liposomal formulations [94, 95]. Size of liposome is the important factors in vivo applications. The size of liposomes affects drug loading, biodistribution, the rate of drug clearance from the body, targeting efficacy to specific organs, and therapeutic [96].

Nanoencapsulation is the inclusion of bioactive substances or entrapment of natural compounds in carriers of nanoscale dimensions. This drug delivery method aims to enhance the solubility of various active pharmaceutical ingredients (APIs) and improve stability by shielding them from harsh environments [97]. This modification of phospholipids enhances self-sealing properties in liposomes and aqueous materials. It expands their applications across diverse fields including agriculture, food processing, cosmetics, tissue engineering, and pharmaceuticals. Phospholipid modification serves as an encapsulation structure for modifying, protecting, and targeting the delivery of essential bioactive compounds in cancer therapy [98].

Nanocarriers are extensively utilized in formulation and development for their various advantages in drug delivery. They serve as a potent method to enhance bioavailability and solubility, prolong drug action duration, and enhance drug stability. Nanoliposomes can be achieved through passive loading encapsulation, where compounds are trapped during vesicle formation: hydrophilic compounds in the aqueous phase, hydrophobic compounds in the lipid bilayer, and amphiphilic molecules in the lipid-soluble region between bilayers. On the other hand, active or remote loading entails trapping bioactive compounds within intact vesicles. This process leverages ammonium sulfate and calcium acetate to enhance encapsulation efficiency, allowing higher drug-to-lipid ratios through pumping or forcing mechanisms while ensuring controlled release by locking bioactive compounds inside the liposomes (Fig. 2B) [41, 98, 99].

2.5.4 Liposome as drug delivery for skin diseases

Topical administration of antibiotics is a common method to treat bacterial skin infections. It is convenient and less invasive compared to other treatments, efficiently accessing various skin layers. Treating a local insect bite infection with a topical antibiotic ointment is often faster and has fewer side effects than oral treatments, as it minimizes the number of drug molecules reaching the target tissue. Additionally, the topical route is cost-effective [100, 101]. The increasing issue of antimicrobial resistance poses a significant threat to antibiotics across all classes, particularly affecting Gram-negative bacteria. These bacteria can undergo complex processes to enhance their defense against antibiotic penetration, particularly within the cell membrane system. In contrast to Gram-positive bacteria, Gram-negative bacteria feature two distinct membrane layers: an outer membrane rich in a thick lipid component called lipopolysaccharide (LPS) and an inner cytoplasmic membrane abundant in

peptidoglycan. These robust components effectively hinder polar molecules while exhibiting greater lipophilicity (Fig. 3A and B) [102–104]. Therefore, a strategy is needed to enhance bacterial eradication and decrease resistance cases effectively. Different vehicles like ointments and gels can transport antibiotics for topical administration. However, developing a durable and effective drug formulation can be a time-consuming process [89]. Many scientists combine natural-derived compounds with antibiotics to generate innovative ideas. Lipid-based drug carriers like liposomes are favored for their ability to penetrate deep into bacterial cytoplasm [105]. Hydrophilic drug molecules typically carry a positive charge that hinders bonding with the bacterial outer membrane. Bacterial cell membrane sizes, primarily composed of lipid structures, vary based on their chemical composition. Gram-positive bacteria possess a thicker cell wall (20–80 nm) compared to Gram-negative bacteria (< 10 nm) [106, 107]. The outer membrane of Gram-negative bacteria, rich in lipoprotein components (~ 70%), allows small molecules like amino acids and sugars to permeate via specific channels called porins. Similar to bacterial characteristics, liposomes also consist of two distinct lipid layers, enhancing their capacity to fuse together [49].

For effective permeation through the skin barrier, it is essential to consider the size of the drug molecule and its carrier. Drug carriers larger than 300 nm in diameter will likely face challenges passing through skin pores [108]. Liposomes have various sizes. Small unilamellar vesicles (SUVs) are 25–50 nm in diameter, large unilamellar vesicles (LUVs) range from 50–500 nm, and large multilamellar vesicles (LMVs) are 500–10,000 nm in diameter. Smaller liposomes are generally more efficient, making LUVs the preferred size. LUVs, containing phosphatidylethanolamine, enhance liposome penetration by easily fusing with skin lipids (Fig. 4) [109]. Cholesterol is usually provided to ensure liposome stability. With its unique physiochemical characteristic, it is important to assess whether each loaded drug molecule is well capsulated. Various specific drug-trapping methods have been reported. However, each drug may generate different results. The main principal to obtain successful preparation is to elicit drug's solubility and to find a perfect homogenous compound. Theoretically, lipophilic drug molecules can be retained within the lipid bilayer compartment of the liposome, whereas hydrophilic ones blend easily in the aqueous phase [110]. In addition to liposome flexibility in size, a key objective in topical drug delivery is to minimize allergic reactions to the compounds. Skin irritation often arises from chemical substances like surfactants. Lipid-based materials generally induce fewer side effects on the local immune system. In a study by Wu et al. [111], licorice flavonoid licochalcone A loaded into keratin liposomes (LAL) demonstrated a range of benefits for guinea pig skin. Skin irritation tests revealed no visible signs of local inflammation after application to hairless skin during three observation periods. Further analysis indicated a significant distribution of loaded substances in the skin tissue, with LAL showing higher fluorescence intensity compared to the non-liposome group [111].

Understanding the basic pharmacokinetics of specific antibiotics, particularly in topical administration, is as important as selecting appropriate delivery materials. Fluoroquinolones and aminoglycosides are concentration-dependent antibiotics that require peak concentrations to effectively eliminate targeted bacteria. Dosing issues often correlate linearly with toxic effects; higher doses lead to greater side effects. The goal is to maximize pharmacological benefits while minimizing dosage. Incorporating antibiotics into liposomes, especially in nanosized forms, is feasible. β-lactams, on the other hand, are often time-dependent antibiotics. To ensure their full bactericidal potential, frequent systemic release is necessary after administration. Timing plays a vital role in maintaining the required drug concentrations. However, maintaining a stable plasma concentration of antibiotics requires a consistent environment, but the human body's complexity can lead to changes based on specific conditions. Addressing these changes is crucial. Compact carriers like liposomes can enhance stability and phagocytic activity for improved efficacy. In topical applications, the focus is on optimizing the permeation system to prevent inadequate antibiotic concentrations in plasma, which can elevate resistance risks. Novel antibiotic discoveries are time-intensive, while mortality rates continue to rise annually. Unlike conventional delivery materials, liposomes enable nanoparticle formulations and robust combinations with various compounds, including polymers and non-organic materials like silver and gold. Sang et al. [7] incorporated polymyxin B (PMB) into a modified liposomal system (P-lipo) and observed that the larger liposome size increased the penetration of PMB concentration into *P. aeruginosa* by interacting with membrane-anchoring lipid A on the outer membrane. In vivo tests supported these findings, showing a significant survival rate of up to 60% in mice injected with D-galactosamine hydrochloride-induced shock septicemia when administered P-lipo compared to the non-liposome group. Overall, P-lipo demonstrated enhanced effectiveness, particularly in terms of its ability to bind with bacterial lipopolysaccharides (LPS) [7].

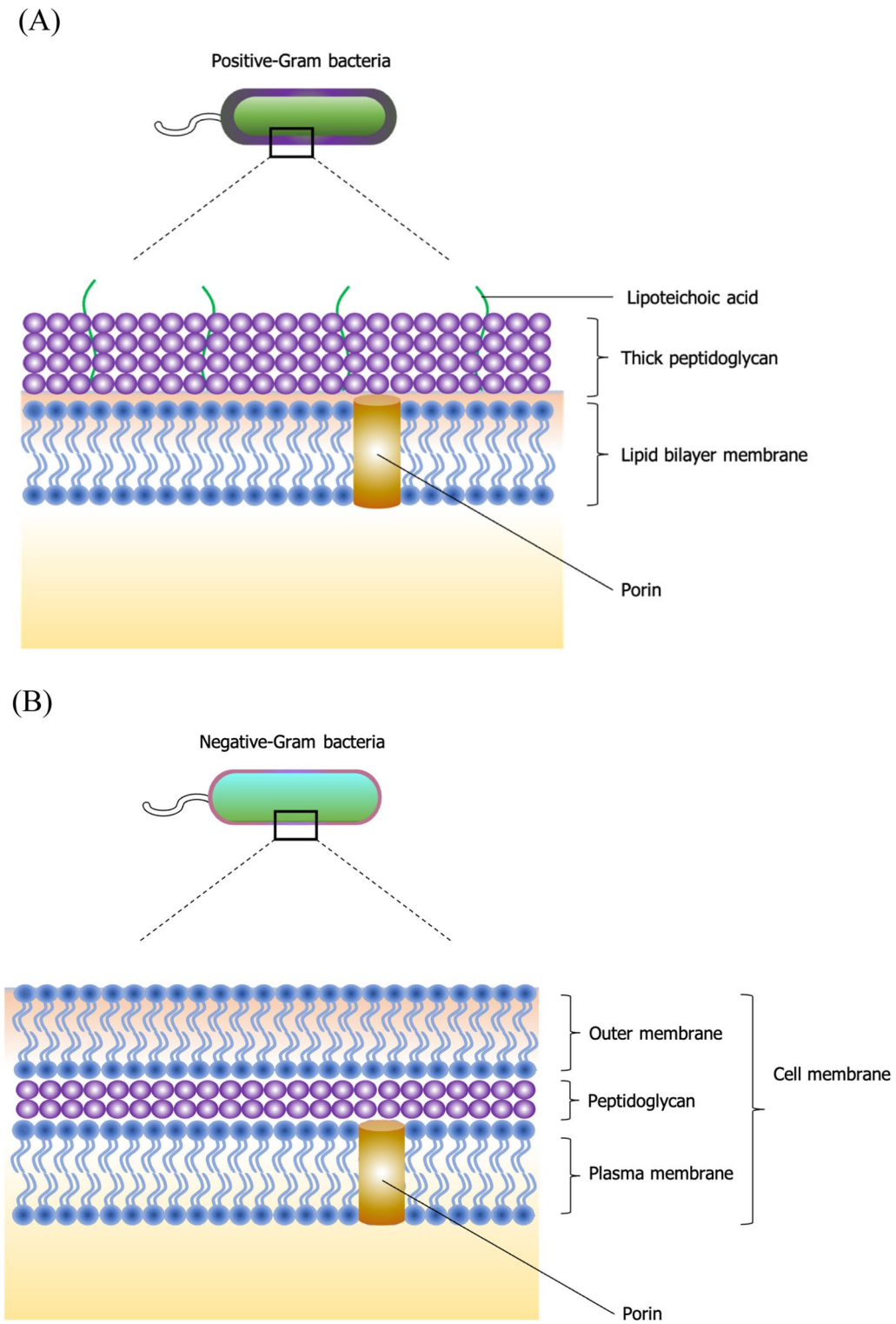


Fig. 3 According to membrane structures, bacteria could be identified as Gram-positive and Gram-negative bacteria. The apparent thick peptidoglycan is shown in Gram-positive bacteria (**A**) and could be seen through Gram staining. Meanwhile, Gram-negative bacteria (**B**) only possesses thinner peptidoglycan wall but has two layers of cell membrane

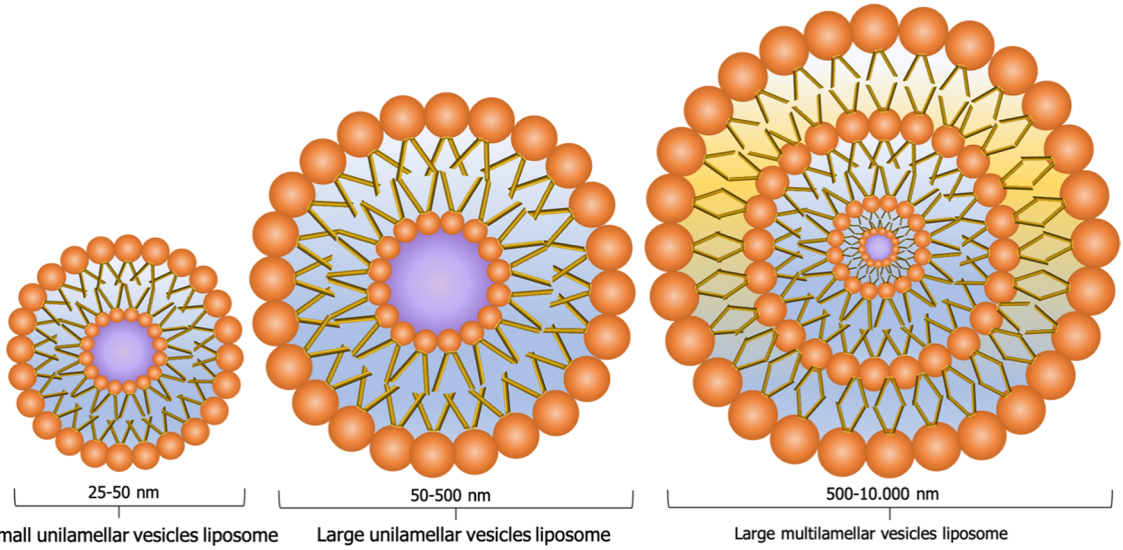


Fig. 4 Three different type of liposome according to its molecule size

2.5.5 Liposome's ability in enhancing antibiotics permeation across skin barrier

Designing drug molecules for gaining the benefits is a challenge. To address the increasing antibiotic resistance, more research is focused on this inevitable event. Skin infections caused by bacterial pathogens such as skin normal flora, *S. aureus* contribute to specific antibiotic resistance called MRSA. The number of MRSA cases continue to increase every year throughout countries, as reported by Centers for Disease Control and Prevention (CDC). More than 70,000 severe infections and nearly over 9000 deaths per year have been recorded [113, 114]. The basic characteristic of MRSA is its ability to resist most beta-lactam antibiotics such as flucloxacillin, methicillin, oxacillin, and cefoxitin. The bacteria is often present in the pus of diabetic foot ulcers or chronic impetigo. However, vancomycin, the preferred treatment, is limited and inaccessible in many low- and middle-income countries [115, 116]. Unfortunately, more vancomycin-resistant *S. aureus* infections have been found in the last two decades with at least 11 *van* gene clusters that contribute to the resistance process (VanA, VanB, VanD, VanF, VanI, VanM, VanC, VanE, VanG, VanL, and VanN phenotypes). To eliminate further infections, CDC recommends systemic antibiotic for vancomycin-resistant *S. aureus* (VRSA) [117]. A new breakthrough in drug delivery systems allows the combination of multiple antibiotics in one carrier, including drugs from different antibiotic classes and natural substances. Given the increasing adaptability and resilience of pathogens against antibiotics, additional strategies are essential to mitigate potential harm, such as designing improved vehicles for delivering antibiotics [113, 118, 119].

The increasing research interest in liposomes as futuristic drug carriers not only enhances medicine significantly but also meets high demand for improvements. In dermatology, liposomes are extensively utilized in various drug formulations like ointments and gels. The primary concern is maintaining stability for effective penetration through skin layers. Nanopharmaceuticals aid in addressing this challenge by chemical manipulation of liposomal profiles [120, 121]. Liposomes, rich in lipid content, can penetrate deep into skin tissues due to their lipid bilayer structure. Coating antibiotics with liposomes enhances solubility, facilitating efficient transport through the skin with its negatively charged state. Introducing a more positive charge in the design can significantly amplify the visible effects (Fig. 5) [47, 122].

Liposomes can enhance the antibiotic's ability to penetrate infection sites compared to antibiotics alone [38, 112]. Chloramphenicol-loaded DA (deoxycholic acid) liposomes double the chloramphenicol concentration deposition in the follicular level of nude mouse skin compared to an aqueous control group, with 5.8 μg/cm^2 in the stratum corneum versus 4.6 μg/cm^2 for chloramphenicol alone [123]. Nanosized liposomes demonstrated superior results. A study assessing nanosized rifampicin against *S. aureus* displayed enhanced bacterial colony reduction relative to rifampicin alone by the fifth day. Adding cationic lipids like monoolein (MO) and *N*-[1-(2,3-dioleoyloxy)propyl]-*N*,*N*,*N*-trimethylammonium methyl-sulfate (DOTAP) (NanoRIF) increased rifampicin's cytotoxicity toward *S. aureus.* Mice treated with 25 mg/kg NanoRIF showed significantly fewer or undetectable bacteria ($p < 0.05$) compared to the untreated group, with the 12.5 mg/kg group exhibiting

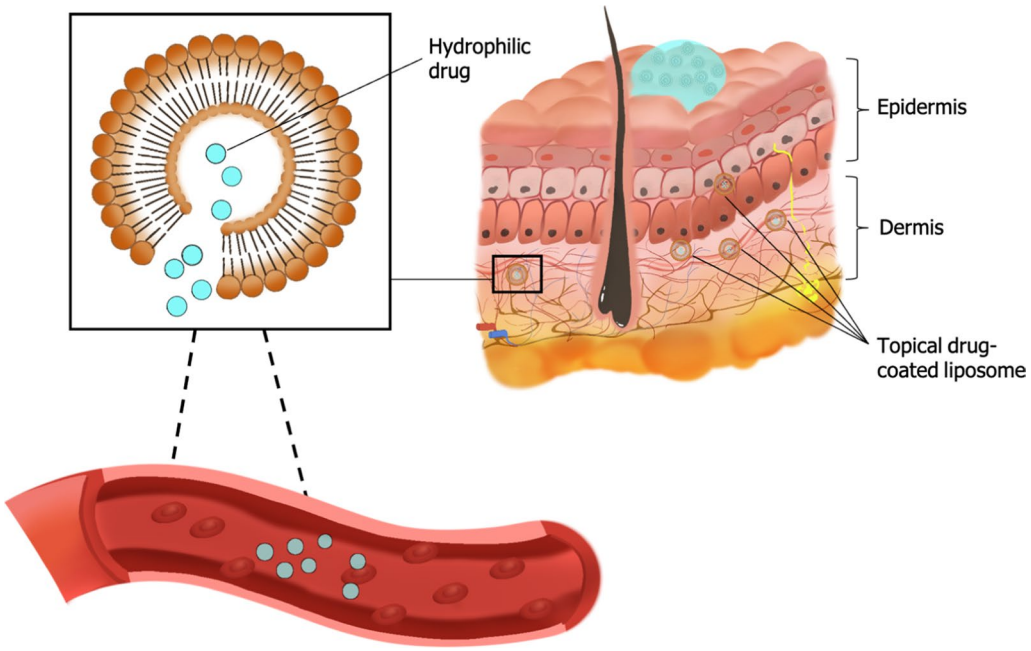


Fig. 5 Entrapment ability of liposome to coat various drug molecules increases the bioavailable of drug and further enables higher plasma concentration with as smallest dosage given as possible

even better average reductions [105]. An additional strategy to improve sustained drug release from liposomal carriers involves combining them with water-based gel formulations. Liposome-in-hydrogel formulations demonstrate enhanced membrane-active antimicrobial activity compared to Chlorhexidine alone [124]. Another study indicates that loading vancomycin into liposomes enhances the phagocytic ability of cultured leukocytes against *S. aureus.* Overall, topical nanoliposomes are preferred due to their potential for recognition by bacterial cell walls through endosomal mechanisms and reduced interaction with natural biofluid [125].

2.6 Current research: in vitro and in vivo

2.6.1 Fusidic acid

Fusidic acid (FA) is a broad-spectrum antibiotic primarily used to treat various pyoderma types caused by Gram-positive bacteria, including impetigo, erythrasma, bullous impetigo, psoriasis, folliculitis, furuncles, carbuncles, and infected wounds and burns. This antibiotic, known for its low water solubility and steroidal effect, shows decreased drug concentration over time if given systemically (orally or via injection), partly due to associated adverse reactions. The topical route is often preferred due to higher patient compliance [126, 127]. Mutations in different nucleotides of the bacterial protein synthesis gene, fusA, pose an increased risk that can arise from irrational usage [128, 129]. Using nanotechnology to enhance fusidic acid (FA) bioavailability is evident in its encapsulation within nanoemulsions. Nanoemulsions (NE) are a type of nanolipid formulation, akin to liposomes, niosomes, and ethosomes. Encapsulating FA with NE leads to a significantly higher release rate ($p < 0.05$) compared to NE-hydrogel formulations, likely due to the presence of FA in the outer aqueous phase of the NE formulation, facilitating easier and greater drug release. In optimized NE formulations, approximately 90.66 ± 3.43% of FA is released within 6 h. The antibacterial activity against *S. aureus* was assessed using the disk diffusion test, showing a larger killing zone with FA-NE compared to blank FA and NE formulations alone [130]. Encapsulating fusidic acid in niosomes has shown promising results, as reported by Waqas et al. [130]. The size of FA when formulated with niosomes ranges between 377.2 and 725.4 nm. The smaller size of niosome-loaded FA may be attributed to the high cholesterol content, which increases surface energy and reduces particle size. Skin permeation studies reveal a significantly higher flux rate in an ex vivo model of mice skin with niosome-loaded FA (80.02 μg/cm^2/h) compared to blank gel alone (15.98 μg/cm^2/h) [127]. Another study compared the permeation profiles of FA in liposomal gel to plain FA hydrogel and creams. Over a 24 h period, approximately 75 ± 1.2% of FA was absorbed into the mice skin. Furthermore, retention tests showed higher values (1.620 ± 0.8 mg/cm^2) compared to commercial cream (0.476 ± 1.4 mg/cm^2) and plain hydrogel (0.659 ± 1.6 mg/cm^2) [126].

2.6.2 Daptomycin

While *S. aureus* is part of the human skin microbiome, many skin infections are primarily caused by this bacterium. The clinical severity of such infections varies based on immunity levels. Topical antibiotics offer significant benefits against these bacteria, but excessive and improper use can result in prolonged healing times. Daptomycin is a novel cyclic lipopeptide antibiotic derived from the fungus *Streptomyces roseosporus*, capable of effectively targeting various Gram-positive pathogens, including MRSA, VRSA, vancomycin-resistant *Enterococci* (VRE), glycopeptide-resistant *S. aureus* (GRSA), Coagulase-negative *staphylococci* (CoNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP), *Clostridium* difficile, *Clostridium* perfringens, *Finegoldia magna*, *Bacillus megaterium*, and *P. acnes*. [131, 132].

A study demonstrated the efficacy of daptomycin-loaded flexible liposomes using a diffusion cell method against *S. aureus* until visible biofilm formation occurred. The cell viability ratio of the control group to the experimental group was nearly $1{:}10^8$. An in vivo experiment comparing control and daptomycin-loaded flexible liposome-treated mice showed that after four days of daptomycin application to the mice's hairless skin, scattered and less visible *S. aureus* biofilm was observed through scanning electron microscopy. However, a similar outcome was noted in the positive control group that received intravenous antibiotic injections [48].

2.6.3 Tetracycline

Acne vulgaris (AV) is a major skin disease that mostly occurs during puberty. Alongside various infection skin diseases such as pyoderma, AV could develop tremendous manifestation starting from blackhead to excessive pustules. The well-known pathogen involved in AV is *P. acnes*. The wide range of clinical appearance in AV requires different medications. Topical antibiotic is one of the most applied medicines to treat such disease. Tetracycline family is considered to generate great magnitude of bactericidal activity and acts by inhibiting bacteria' protein synthesis process [133, 134]. Specifically, tetracycline could disable the chemotaxis mechanism of neutrophils induced by *P. acnes* and reduce Interleukin-8 (IL-8) expression and phospholipase A2 to reactive oxygen species production [135].

Eroğlu et al. [54] reported that using tetracycline HCl and tretinoin-loaded hydrogel liposome on *S. aureus* and *S. epidermidis* significantly reduced bacteria life growth. The MIC was slightly different between non-hydrogel and hydrogel formulations, with the non-hydrogel showing a lower MIC compared to the hydrogel formulation.

2.6.4 Rifampicin

The skin plays a vital role as a protective barrier for the body. Any disruption in skin continuity, whether traumatic or not, can compromise immunity against external threats like pathogen infiltration. Rifampicin is known for its broad-spectrum antibacterial effects, targeting bacterial RNA synthesis. Specifically, rifampicin binds to the active site of RNA polymerase, inhibiting RNA elongation [136]. It is commonly utilized in treating chronic wounds, particularly those associated with progressive infectious skin conditions like diabetic ulcers. However, achieving a stable topical form of this antibiotic requires further research, especially in finding suitable drug delivery methods. Wallenwein et al. [137] conducted a study on encapsulating Rifampicin in nanoliposomes under an oxidative stress model. Wounds that are damaged or heal slowly often involve oxidative processes. When compared to ascorbic acid, rifampicin-loaded liposomes demonstrated similar efficacy in reducing oxidation levels and protecting rifampicin from lysosomal degradation. Additionally, higher levels of oxidation products resulted in more rifampicin molecules being released from the liposome vesicles [137]. Another study showed that rifampicin-loaded liposomes exhibited greater efficacy in killing *Mycobacterium abscessus* compared to a group without the antibiotic encapsulated in liposomes [138].

2.6.5 Amphotericin B

Cutaneous leishmaniasis, affecting nearly 700,000 to 1 million people annually, is primarily caused by the protozoan parasite *Leishmania* from the *Trypanosomatidae* family, leading to skin ulcers. Amphotericin B, a second-line antibiotic for leishmaniasis, acts by inducing membrane cell leakage in protozoa. Amphotericin B, a second-line antibiotic for leishmaniasis, acts by inducing membrane cell leakage in protozoa [139]. To get a greater effect against *Leishmania* protozoa, the topical route is the most convenient and least toxic method of administration. Smaller particle sizes are preferable for topical skin drugs. In a study by Jaafari et al. [140], the efficacy of amphotericin B-loaded liposomes (Lip-AmB) in killing *Leishmania major* protozoa infecting cultured macrophages was investigated. The experimental group demonstrated non-inferiority in suppressing protozoa viability compared to Fungizone© as the positive control. Notably, significant results were observed in an in vivo study. After 8 to 12 weeks of exposure to Lip-AmB 0.4%, the parasitic count in the mice spleen was significantly lower than in the placebo group ($p < 0.001$) [140].

2.6.6 Azithromycin

S. aureus is a prevalent skin microbiome, contributing to approximately 76% of various skin infection diseases, particularly pyoderma. In cases of diabetic ulcers, bacterial infiltration into deeper skin layers can exacerbate the condition. This bacterium typically colonizes the superficial skin layer and adheres to corneocytes. Besides pyogenic skin lesions, *S. aureus* is recognized as a contributing factor in atopic dermatitis (AD) [141, 142]. Azithromycin is a macrolide antibiotic which disrupts bacterial protein synthesis by binding near the peptidyl transferase center on 23S rRNA [143]. Pathogenic bacteria are the main targets of this antibiotic. However, the rise of MRSA cases globally raises concerns for clinicians due to significant cost implications. MRSA contributes to community-acquired nosocomial infections and increased morbidity and mortality from multidrug resistance (MDR). Several studies have highlighted that azithromycin's poor water solubility makes it challenging to find effective carriers. Microemulsions represent one strategy to enhance azithromycin penetration into skin tissue [144, 145]. Another strategy is loading the antibiotic into liposomes. Rukavina et al. [47] investigated the efficacy of azithromycin-loaded liposomes in treating MRSA infections and analyzed their permeation through porcine ear skin. The study revealed that azithromycin-loaded liposomes inhibited about 90% of bacterial growth at concentrations ranging from 0.5 to 8 µg/ml, compared to free azithromycin requiring higher doses (8 to 32 µg/ml) to achieve a similar effect. The primary objective of topical drugs is to attain maximum concentrations at the target site while preventing excessive penetration beyond the superficial tissue layer. The experiment demonstrated that entrapping the antibiotic within cationic liposomes (CATL) optimized drug concentration in the stratum corneum by approximately 35%, whereas free azithromycin was more concentrated in deeper skin layers [47].

3 Conclusion

Bacteria primarily consist of essential macromolecules like lipids, proteins, and glycans. Antimicrobial agents are designed to target crucial components of bacteria's machinery system, disrupting them by interacting with specific ligands or receptors both inside and outside the bacterial cell. Nevertheless, the increasing survival rates of bacteria and the indiscriminate prescription of antimicrobials have contributed to a higher prevalence of antimicrobial resistance. To eradicate pathogenic bacterial colonies in the human body, multiple factors are essential. Irregular dosage regimens, delayed medication intake, and abnormal health conditions can alter the normal pharmacokinetics of antimicrobial agents. For instance, insufficient plasma concentrations compared to the bacteria's MIC can promote further resistance. The challenge of antimicrobial resistance is widely acknowledged by scientists as unavoidable. Consequently, innovative breakthroughs are imperative for future solutions [146–148]. Recently, futuristic drug delivery system has become more popular. Liposomes enables higher intracellular drug loading due to their nanosized design and adaptability. Liposomes are rich in phospholipids, thus they easily penetrate tissues with lipid bilayer structures. Additionally, liposomes can incorporate a variety of organic and non-organic molecules like silver, gold, and magnets. The primary goal is to achieve efficient and optimal internalized drug concentrations to effectively combat pathogenic bacteria. While many liposomal products have been approved by FDA for clinical use, their application is predominantly limited to systemic and transdermal routes. The utilization of topical liposome drug delivery, especially for antibiotics, is not yet widespread, likely due to ongoing studies. However, topical application is known for being noninvasive, convenient, and effective in treating skin infections. Misuse and overuse of this delivery system may contribute to the rise of antibiotic resistance. Some studies suggest that there is no significant difference between applying postsurgical topical antibiotics alone and non-antibiotic agents like paraffin or petrolatum for infection prevention. Although achieving efficient drug absorption poses complexities in pharmacokinetic studies, the key principle is to administer the smallest effective dosage possible or opt for the minimum therapeutic dose [13, 35, 149, 150].

In conclusion, the use of liposomes to improve the permeation of antimicrobial drugs for topical applications holds promise in addressing antibiotic resistance. More studies are required to strengthen the findings, continued with clinical setting research.

List of abbreviations

MIC	Microbial inhibition concentration
OTC	Over the counter
P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*
E. faecalis	*Enterococcus faecalis*
S. viridans	*Streptococcus viridans*
E. coli	*Escherichia coli*
H. influenza	*Haemophilus influenza*
TDDDS	Topical dermal drug delivery systems
SC	Stratum corneum
K	Partition coefficient
D	Diffusion coefficient
C_{max}	Maximum drug concentration in the skin layers
T_{max}	Time required to reach C_{max}
AUC	Area under the curve
AuC	Gold nanoparticles
FDA	Food and drug administration
TH	Liposome: terbinafine
CFU	Colony-forming units
CDC	Centers for disease control and prevention
TEWL	Transepidermal water loss
dOFM	Dermal open-flow microperfusion

P. acnes	*Propionibacterium acnes*
MRSA	Methicillin-resistant *S. aureus*
S. epidermidis	*Staphylococcus epidermidis*
PK	Proteinase K
RA	Retinoic acid
SME	Soyethyl morpholinium ethosulfate
SD	Standard deviation
CPT	Cryptotanshinone
RES	Reticuloendothelial system
NISV	Non-ionic surfactant vesicle
VISA	Vancomycin-intermediate *S. aureus*
API	Active pharmaceutical ingredients
LPS	Lipopolysaccharide
SUVs	Small unilamellar vesicles
LUVs	Large unilamellar vesicles
LMVs	Large multilamellar vesicles
LAL	Licochalcone A-liposome
P-lipo	Polymyxin B (PMB)-liposome
VRSA	Vancomycin-resistant S. aureus
DA	Deoxycholic acid
MO	Monoolein
DOTAP	N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate
NanoRIF	Monoolein (MO) and N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate (DOTAP)
NE	Nanoemulsions
FA	Fusidic acid
S. roseosporus	*Streptomyces roseosporus*
VRE	Vancomycin-resistant enterococci
GRSA	Glycopeptide-resistant *S. aureus*
CoNS	Coagulase-negative *Staphylococcus*
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
AV	Acne vulgaris
M. abscessus	*Mycobacterium abscessus*
IL-8	Interleukin-8
CL	Cutaneous leishmaniasis
Lip-AmB	Amphotericin B-loaded liposome
AD	Atopic dermatitis
MDR	Multi-drug resistant
CATL	Cationic liposome

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