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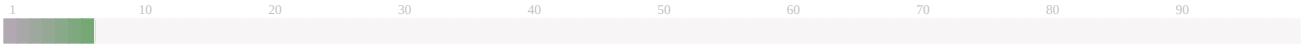

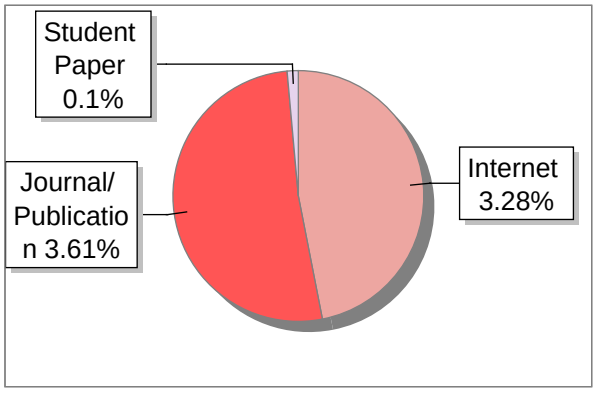

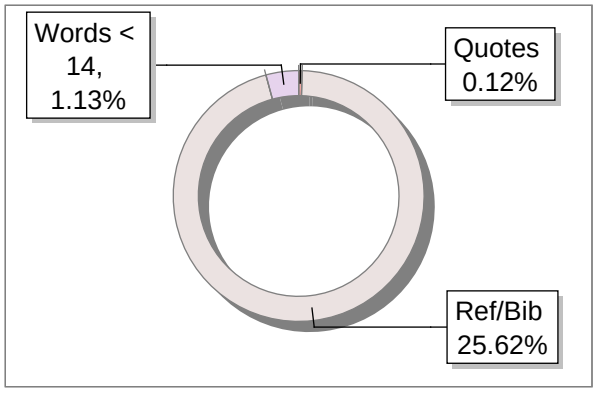

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Cover letter

March 27, 2024

Editorial Department of Asian Journal Pharmaceutical Sciences

Shenyang Pharmaceutical University

No.103, Wenhua Road, Shengyang 110016, China

Dear Editor of AJPS,

I am submitting a manuscript for consideration of publication in Asian Journal of Pharmaceutical Sciences. The manuscript is entitled "Current pharmaceutical breakthrough : Liposome encapsulation to enhance antibacterial activity to treat topical infection disease".

It has not been published elsewhere and that it has not been submitted simultaneously for publication elsewhere.

Our review mainly talks about the advantageous of liposome as drug delivery for topical antibiotics. The application of drug-coated nanoliposome has been well known to carry out Doxorubicin (Doxil®) to treat cancer. However, not many current studies reported observing and analysing it especially when it's formulated altogether with antibiotics. With the rising cases of antimicrobial resistance, achieving effective and efficient plasma concentration is more favourable amongst other options. In addition, many skin infection caused by bacteria may harm further area even deeper into the systemic. Therefore, this review helps to provide better understanding in regards of liposome as nanocourier for topical antibiotics.

Thank you very much for your consideration.

Yours Sincerely,

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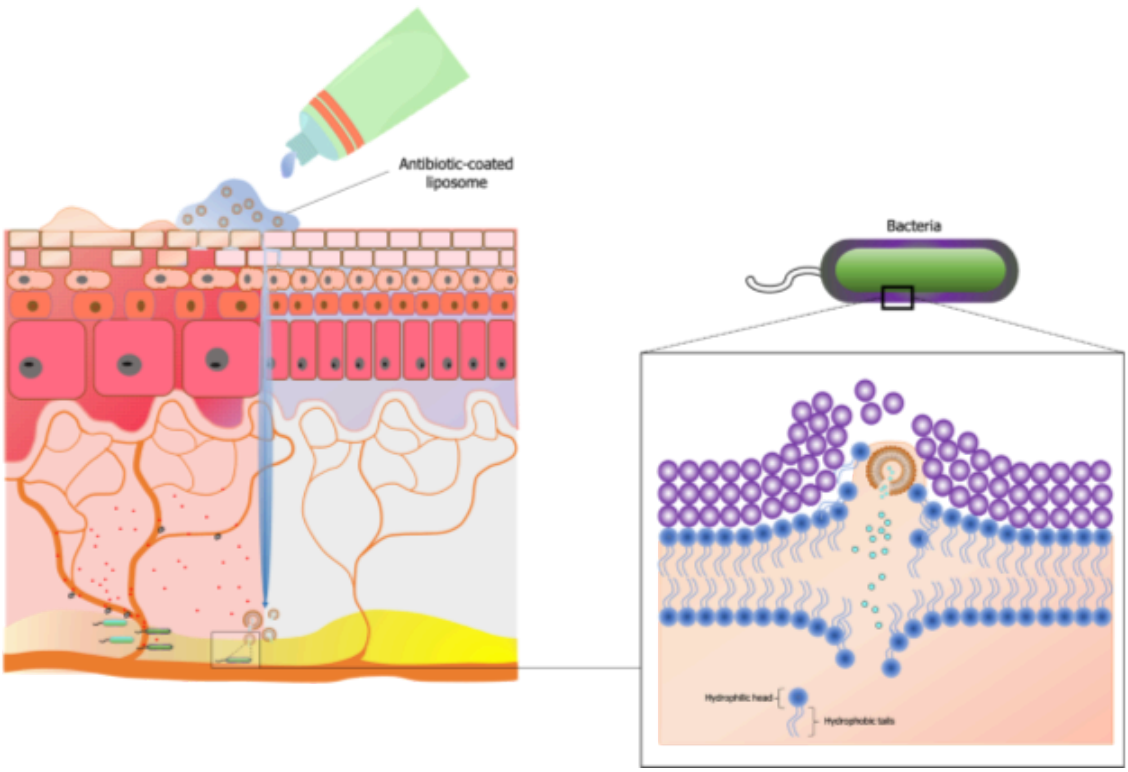
Graphical Abstract (without Author Details)

Topical antibiotic encapsulated by liposome allows better releasing of the drug molecule into systemic blood vessel through permeation system of the skin tissue. Liposome mimics similar characteristics with human and bacteria bilayer membrane surface, with hydrophobic and hydrophilic parts. Nanosized liposome also enhances the mechanism. Thus, higher plasma concentration could be achieved to kill the bacteria effectively.



Title Page (with Author Details)

Current pharmaceutical breakthrough : Liposome encapsulation to enhance antibacterial activity to treat topical infection disease

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Current pharmaceutical breakthrough : Liposome encapsulation to enhance antibacterial activity to treat topical infection disease

Abstract:

Rising trend of antibiotic resistance in the future always challenges scientist especially in developing better drug formulation. New antibiotic discovery could take years to find, thus managing ideal drug delivery system has become main focus nowadays. Furthermore, topical usage of antibiotic is often yet sometimes neglected in terms of side effects. Liposome, with ability to mimic natural physiochemistry properties of human cells has allowed greater shortcut to reach in intracellular efficiently. In this review we discuss mainly about the liposome adaptability form when it encapsulates various antibiotics from many recorded and recent studies. In addition, we also highlight how liposome could provide enhancement to topical antibiotic as well as inhibition ability toward bacteria compared to unloaded one. We also aim to raise more knowledge in regards pharmaceutical breakthrough with liposome as nanocourrier for topical antibiotics.

Highlights

- Liposome body contains both hydrophilic and hydrophobic components as human lipid bilayer system. It allows greater permeation especially to tissues with high phospholipid compounds, such as skin tissue. Major breakthrough liposome has provided majorly related to better uptakes of small molecules substances, with no exception of drug molecules.
- Skin tissue is considered complex for its barrier function capacity to protect further inside of body. Small, unilamellar vesicles (SUVs) is known for its remarkable size and allowing drug absorption efficiently. However, in terms of killing bacteria colonies require more than just size.
- Bacteria adaptability to survive from robust antibiotic classes define the magnitude of challenges. Liposome answers the challenges by giving flexibility for it enables drug releasing effectively. Thus, it creates good benefits to catch maximum potential in decreasing more bacteria growth.

Keywords: Liposome, Nanomedicine, Skin infection, Topical antibiotics

1. The anatomy and histology of skin

The skin is the widest organ that cover the body. It has functions as physical barrier, sensory, and immunology. It accommodates homeostasis by limiting the loss of water, electrolytes, and heat. It contains of merkel cells as mechanoreceptor and also Langerhans cells or dendritic cells as immune system [1,2]. Skin tissue is mainly divided into 3 different layers (Fig. 1). They are epidermis (the outermost), dermis, and hypodermis (subcutaneous layer). Epidermal layer is arranged from squamous epithelium and is subdivided according to the degree of keratinization of the cells. The layers are stratum basale (consist of basal cells) in the bottom, the stratum spinosum (consist of spinous or prickle-cells), stratum granulosum (consist of granular cell), and stratum corneum (consist of corneocytes). Stratum corneum are united by lipid bilayers assembled into a brick and mortar arrangement [1,3]. In stratum basal, the cells are actively proliferated, undergo changes become keratinization and moves outwards towards stratum corneum. Stratum corneum forms hydrophobic layer with 10-30 μm thickness and commits as prominent barrier for skin permeation. Besides the corneocytes, the barrier made up by extreme lipid component which are keratin filaments and filaggrin. Corneocytes are embedded in multilamellar lipid including lipid-like sterols, phospholipids, and glycosphingolipids [2].

The deeper layer below epidermis is dermis. The thickness of dermis is 3-5 mm and it consist of mixture of fibrous protein (such as collagen and elastin) and an interfibrillar gel of glycosaminoglycans, salts, and water. It also contains appendages including sweat gland, pilo sebaceous units, blood vessel and nerves. The function of dermis is to provide support binding between epidermis and subcutis, keep the tensile strength, elasticity and resilience [2], it also supports nutrient and oxygen delivery and waste removal from epidermis by diffusion across dermo-epidermal junction [4]. Dermis is also contains range of immune cells including macrophages and dermal dendritic cells. The dermis provide the route of permeation of drugs via transcellular route (diffusion across corneocytes), intercellular route (diffusion across the lipid matrix), and the shunt pathway or appendageal route (diffusion into sweat gland, hair follicle, and sebaceous gland) [2].

The hypodermis layer is formed from loose connective tissue and fat. The component in dermis and hypodermis are blood vessel, lymphatics, nerve cells, and also skin appendages. The surface are covering by the appendages is only about 0.1% of the skin continuum [2].

Although the absorption of compound is little, this route enables permeation of charged molecules and large polar compounds; e.g., peptide-based drugs [5].

2. The permeation system in skin

Understanding the skin permeation system is important before formulating the suitable topical drug delivery. Skin is the first barrier to provide strong immunity protection toward various threats from environment such as biological, mechanical, chemical and physical attacks [6]. Overall width of skin tissue could elongate to approximately 2 m^2 and divided into several layers. Each layer has specific functions according to its histological feature. Form outward to inward, skin tissue comprises of living epidermis, dermis and hypodermis layers. Epidermis structure is arranged by five different layers, stratum basal, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. The notable stratum to be considered for topical route administration is stratum corneum [6,7]. Prior the permeation process, the important variable that must be considered is the partition phenomena. In terms of drug pharmacokinetic, partition relates to distribution system of the drug. The partition phenomena occurs between the drug vehicles and the surface of the skin tissue to finally achieve the equilibrium. During the process, diffusion and partition will repeatedly take place until the whole drug molecules completely reach the capillary system. In order to define the partition potency, it requires an absolute value which furtherly explains the ratio number between the two involved variables. Partition coefficient (K) helps to determine the strategy to increase the ability of drug absorption through skin barrier especially if the drug is designed as transdermal route [8,9]. As the definition, K is a value to estimate the drug concentration of certain skin route drug toward its delivery system [10]. In regards of obtaining the said coefficient, various study to retrieve the information have been conducted previously. In a study using human viable epidermis and stratum corneum layers, the partition coefficient is obtained by measuring the concentration of drug compound contained 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). Another study states the partition coefficient is 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 suggests K value is found higher in lipidized sample than the delipidized stratum corneum (fully hydrated). The size of compound that less than 500 Da is

considered to easily penetrate through passive diffusion across lipid bilayer of cell membrane and furtherly passes the absorption step [11]. Aside of partition coefficient, another important parameter needed to observe and analyze skin penetration ability is diffusion coefficient (D). The diffusion coefficient is obtained by measuring the steady flux values and its lag times. However, only several studies have been reported the diffusion coefficient of the skin since the model and method are limited. Both parameters eventually could be used to calculate the rate absorption of the skin [12].

The stratum corneum of the skin is the main location for percutaneous drug absorption since it consists of corneocytes and enriched with intercellular lipids thus it elicits hydrophobic ability. The corneocytes are connected through desmosome to ensure the strength of tissue connectivity and permeability capacity for most hydrophilic molecules greater than 200-350 Da [13]. The intercellular lipids form such a matrix which contains stratified hydrophilic and hydrophobic layers and arranged into thick layers as multilamellar sheets [6,8,14]. Due to the rich staggered corneocytes available in stratum corneum, the opportunity for lipoidal diffusion to occur is notably high yet it results to be approximately 1000 times more hydrophobic [6]. By function, the stratum corneum provides the moisturization of the outermost layer of the skin. The significant loss of total body water could lead to dry skin in which affects the drug ability to permeate. Various known routes for drug molecule to access systematic circulation are intracellular, intercellular and transfollicular routes [13]. However, the basic mechanism of permeation system usually depends on the physiochemical appearance of the drug molecules. Highly hydrophobic drugs are difficult to permeate through the hydrophilic layer and vice versa [13,15]. The difference between the available routes is mostly related to the size and solubility to lipid of penetrated molecules. Hydrophilic compound most likely to the 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 [6,13,16]. Unlike the intercellular pathway, the intracellular pathway initiates diffusion that allows the molecules to run deeply into the keratin [6]. 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 [8].

3. Pharmacokinetics of topical drugs to cross the skin barrier

After a topical preparation applied to the skin, the drug must be able to penetrate deeper layers by crossing the various layers above it [17]. Therefore, only a small drug concentration can penetrate the skin layers within a certain period [18]. The dermatopharmacokinetic concept emphasizes three mechanisms, namely: 1) The role of 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; 3) The drug concentration in the skin layers (stratum corneum, epidermis, dermis) describes the dermatological effectiveness of the drug [17]. According to Kalia and Guy (2001), the process of delivering drugs to the skin involves several processes: a) releasing the drug from the dosage formulation; b) the drug penetrates the stratum corneum; c) diffusion of the drug across the stratum corneum, mainly through intercellular lipids; d) separation of the drug from the stratum corneum into the active epidermis layer; e) diffusion across the epidermis layer to the layer below (dermis), and f) drug absorption by capillaries, which reach the systemic circulation [19].

The skin has three layers: epidermis, dermis, and subcutaneous tissue. The epidermis layer consists of several layers, starting from the outermost layer, are the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Corneocytes and lipids in the stratum corneum have a dense brick-and-mortar-like structure as a barrier to permeation and diffusion when administering topical and transdermal preparations [17]. The skin permeation route involves the passage of the drug across the epidermis and skin appendages, mainly hair follicles and sweat glands, which form an alternative pathway to the intact epidermis. The skin appendages cover 0.1% of the human skin surface [19,20]. The outermost layer of skin (stratum corneum) is a barrier structure that can inhibit skin absorption of topical products. However, the essential outer physical barrier contains non-living components (called "dead") [21]. The stratum corneum cells are called corneocytes. Corneocyte cells have a solid structure, are not functional (dead), have a nucleus, and contain keratin [19]. The subcutaneous layers, 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). In the stratum corneum, all corneocytes are flat hexagonal and parallel to the skin surface, have an irregular shape, a diameter of ~40 mm, a width of up to ~1 mm and a thickness of the intercellular lipid area of up to ~0.1 mm. 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. Producing the subcutaneous barrier is influenced by dead corneocytes packaged in a flat, water-resistant sheath in an extracellular lipid matrix by proteolysis corneodesmosomes. These tight molecular structures between corneocytes occupy about 30% of the total surface volume of the stratum compactum corneocytes, namely one per mm2 or 600 to 800 per corneocyte, only 7% of the surface of the stratum disjunctum in non-palmoplantar SC, but >50% in subcutaneous palmo plantar [21].

The 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 SC 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 layer by layer of the skin and be effective for topical treatment. Drugs will more easily pass through the subcutaneous layer if they contain additional formulations in the form of one or more chemicals to increase their penetration ability, have a small molecular weight (molecular weight <~500 Da), have high solubility, and are sufficiently lipophilic (logarithm of octanol partition candidate -water coefficient log P in the range 0 to 5). However, those with a larger molecular weight and are more lipophilic are more difficult to pass through the more watery epidermis due to their poor solubility in water [21,22].

Transportation of drugs in and out of the subcutaneous lipid layer by permeation along the corneocytes is mainly 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 [19,23]. The thick lipid region extends 41 mm between subcutaneous corneocytes, while the thinnest interface is ~ 250 nm long [21,24]. 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 [22–24].

Biopsy results showed >100 lipid bilayers in one location. Corneodesmosomes are distributed in various body locations and can be influenced by the history of treatment 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 [18,24]. 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 10-fold 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. It can be concluded that drug transport through subcutaneous lipids will vary and be influenced by location, be it the depth or location of the subcutaneous SC (at the edge of the corneocyte versus on the surface of the corneocyte) and environmental influences, as well as skin diseases associated with corneodesmosomes [18,20,24].

When initially applied, the drugs will pass through the hair follicles [20]. Drug absorption into the skin is influenced by several factors, namely 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 will mainly affect the diffusion coefficient. Molecules with a size greater than 500 Daltons

will have more difficulty penetrating the subcutaneous. The permeability of drug molecules will be optimal at a lipid/water partition coefficient of 1 or greater. The application of drug formulations with pH levels that are too high or very low can cause skin damage or irritation. Thus, a neutral pH value [usually above the skin's isoelectric point (pH 4)] may be more suitable for topical administration. 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, luminal microflora, etc. In addition, the slow plasma concentration of topical medications can reduce the risk of side effects. Absorption of the drug into the skin occurs through passive diffusion and occurs more slowly. 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 [18].

4. Current available drug delivery for topical route

3.1. As general topical drugs

Topical drugs are a breakthrough treatment with a very low risk of side effects, this is an advantage of topical drug dosage forms. Easy application is the advantage of this form of drug and the high concentration of the drug makes this form often used in long-term treatment [25]. The anatomical structure and physiological processes in the skin that are difficult for foreign substances to penetrate and pass through are a challenge in creating good topical drugs. Classification of topical drug delivery: solid (powder, plaster ointments) semi-solid (gels, ointment, cream) liquid (lotion, solution, emultion, suspension) and miscellaneous (tapes, topical aerosol, rubbing alcohols, liquid clanseer) [26].

Topical delivery system targeting skin melanocytes for whitening, anesthetic for lowering pain, anti-infective agent and activation of Langerhans cells. Skin cell type most important for choosing topical agent or delivery system [27,28]. The earliest method for enhancing skin absorption, now we need some enhance skin permeability without affecting

the skin layer. Four step methods: selection of product, eutectic system, ion pairing, and potential of chemical. There are 2 factors that have an effect on topical drug absorption, namely, first, physiological factors such as thickness, pH and skin type. The second is physicochemical molecular weight and ionization. Topical drug enhancement Directly by: microneedle, biolistic injector, ablation and Indirectly by: electroporation, iontophoresis, sonophoresis [29]. Gels and creams are forms of topical medicine that we often encounter in general. Various optimization efforts on the drug base in increasing the effectiveness of drug penetration into the skin layer by utilizing various agents such as lipids, alcohol, aqueous and protein have produced results [30].

Analogues: nanovesicel is build by bilayer vesicles and made up of lipids, surfactants, alcohol, ethosme, liposome, transfersome, phytoshome, and niosome used to increase skin permeability. Ther parameters: size, composition, drug diffusion skin layer, surface charge and deformability. Nanovesicel Size has a differential effect, such as a nanovesicel grater 600 nm unable to penetrate to deep skin, however nanovesicles with smaller 300 nm have potential to penetrate to deep dermal region [31].

Various known nano couriers [27,29]:

- Microemultion: coolloidal compression molded without energy and stable their prature. Was mixing surfactant, hydrophilic and lipophilic balanced components. Are composed of surfactant, oil, water and cosurfactant with size less than 100 nm. Emulsion enhances permation in skin layer by: high capacity solubilization causes increasing dose application, good skin contact and large area surface, direct permation effect from oil and surfactant. Microemultion is a high potential for topical carrier drugs of skin cancer, skin disorders, and antifungal drugs. The above studies concluded is that the microemulsions have less toxicity and high penetration.
- Nanoemulsion: consist of oil and aqueous system, the homogeneous solution is strengthens, permeability, solubility, durability and bioavailability of the drug functional. Has effective in drug active at therapeutic target organs with less pain. Now the nanoemultion has been used for cosmeceuticals, drugs as pharmaceutical and phytopharmaceutical and nutritional.
- Solid lipid nanoparticle: composed by lipid and thare are solid at room temperature cause surface covering. Enhanced permation by: prolong contact surfactant, oclusive nature

formation cause reduce water losses, lipid interaction with startum corneum lipid facilitating. lipophilic compounds and emultion based, and was considered for antimicrobial agent efficient carrier system. In a study found the SLn has been effective for allergic contact dermatitis delivery of a sustained maner and penetration effect to increase therapeutic effectiveness.

Vesicular drug delivery system such us: liposomes, ethosomes, transferosomes, invasomes, niosomes, SECosomes, PEVs

- Liposome: composed by cholesterol and phospholipids and have more one layer or bilayer structure. Phospolipids are amphiphilic and the main component in liposomes is composed by a non-polar tail and both polar heads. Liposomes can encapsulate bot hydrophlic and lipophilic [31]. are shaped by lipid bilayer but can carry hydrophilic agent of therapeutic betwees core bilayer. Liposome based has been approved and used in medicine since it is nontoxic and most effective than melatonin. Transdermal drug with liposomal based has used examples of diclofenac, ketoprofen and azithromiciyn.
- Ethosomes: main components of the ethosomes are composed by phospholipid mixing alcohol 20-40% like ethanol. Ethanol as a main component in ethosome because there improves the flexibility of penetration enhancer. Ethosome is a nanocarrier with batter drug loading capacity and deformability that is considered superior to liposeme. Modified version of ethosome like transethosome consists of phospholipids, higher ethanol and surfactants. Higger ethanol has action for permeation enhancers, and now transethosome has much interest for transdermal drug delivery. topical delivery system commonly as skin drug, an attractive solution to treat many skin diseases. Ethosome is a lipid delivery vehicle demonstrated better efficiency of percutaneous drug delivery. Rounded vesicles to substance penetrates and deposits at deep skin [27]. Transdermal drugs with liposomal based have used examples of valsartan, econazole nitrate and mitoxantrone. lipid based or phospholipid with ethanol and water, and than used for penetration into deep layers of skin.
- Transfersomes: composed of lipid bilayer with phospholipid, ethanol and aqueous, ther deformity of liposomes an completed with surfactant ratio for skin permeation. Transfersomes have sinific factors from there compound. there is liposome with rim activator as sucfactant, an disrupted lipid bilayer providing flexibility. With that structure

transferosomes as allow penetration in deep layers of skin. flexible carrier midfied from lipid based, can be used for drug medication delivery to deeper layers of the dermis [32].

- Niosomes: are non ionic surfactants, thermodynamically stable and used for control and targeting based drugs. Are have aging size 10-1000 nm its smaller than liposome and better than liposome penetration [27].

3.2. As Topical Antibiotic

Topical forms of medication are the choice for applying antibiotics to visible and superficial parts of the body. The relative advantages of drugs that have specific targets with high concentrations and the possibility of resistance and low side effects are the potential of this form of drug. Generally, topical antibiotics used are in the form of creams and ointments, but there are several other forms of topical medicinal preparations that contain antibiotic substances and compounds such as ointments, solutions and drops [33]. The use of topical antibiotics can be used based on the location and type of disease obtained. In this study, researchers divided them into organ groups in the form of skin wounds, ear infections, eye infections and respiratory infections (Table 1).

- Skin infections

  The skin is the largest part of body after the intestines, its surface is superficial and easily exposed to various substances, making it easier for skin with wounds that are not well maintained to become infected. Burn wounds are wounds with a high potential for microbial infection due to a competition for dominance between infectious microbes and human keratinocytes [34]. The use of topical antibiotics is a 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, the topical antibiotics used work by suppressing bacterial growth and changing the condition of the skin so that it can support the repair of cells in the skin. 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.

- Ear infection

  Ear infections often occur due to an imbalance in the pH and acidity of the ear canal, making it a space for bacteria such as Pseudomonas aeruginosa and Staphylococcus aureus [35]. Using topical antibiotics has the same effect as using oral antibiotics.

Rosenfeld in his research found that the activity of topical antibiotics in ear infections was more effective than oral antibiotics. The use of topical antibiotics in the ear can be done preoperatively and post-operatively as a form of prophylaxis against ongoing infections. The drugs generally used are Chloramphenicol and ciprofloxacin [36].

- Infection of the eye

  Inflammation of the eye can occur due to infection or non-infection, while conditions that commonly occur in infectious eye inflammation are blepharitis, keratitis and bacterial conjunctivitis [37]. The use of topical antibiotics is used in these conditions as treatment and as preoperative and post-operative prophylaxis. This is still a recommendation today even though it is necessary to optimize enhancers and vehicles to solve the challenges of the eye's complex anatomical shape [38].

- Infection of the respiratory tract

  Maximizing drug delivery with topical preparations specifically for inhaling antibiotics has a specific target without reducing the effect and minimal side effects. Rapid and specific treatment of respiratory tract infections with minimal side effects has an important role in reducing symptoms and the risk of complications in sufferers [39]. In general, inhaled antibiotic treatment that has been used, such as aminoglycosides, which can be used in pneumonia conditions, has been widely used and is the initial empiric therapy for sufferers [33].

5. Liposome as strategy to increase nano permeability for topical antibiotics

4.1. Definition of liposome

In 1961, Alec Bangham first created liposomes and its invention has revolutionized the pharmaceutical field. The application of liposome are now established in various area such as drug, biomolecules, and gene delivery. Liposomes are spherical vesicles characterised by a lipid bilayer with an internal aqueous cavity which components are phospholipids or synthetic amphiphiles incorporated with sterols, such as cholesterol, to influence membrane permeability. It has a hydrophilic head and a hydrophobic tail. Liposomes can be formulated and processed to differ in size, composition, charge and lamellarity, and it has become one of the preferred nanocarriers for many biomedical applications. Due to extensive developments in liposome technology, a number of liposome-based drug formulations are available for

human use and many products are under different clinical trials. In 1974, Allison and Gregoriadis liposomes were the first system described to offer adjuvant action with their immunological role and adjuvant properties being identified. The negatively charged liposomes incorporating dicetyl phosphate were able to potentiate immune responses against diphtheria toxoid. Liposomes as adjuvant is limited to two vaccine system, they are Inflexal and Epaxal. The first successful achievement in liposome-based products was the introduction of Doxil® to the U.S. 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 commenced the development of Doxil® in Israel and the USA. It was the first nano-sized liposomal product to obtain regulatory approval [40–43]. As transdermal drug delivery vehicles, liposome has limitation linked to the fact that they tend to adhere to the inside of the skin cell walls, causing the collapse of phospholipid-associated bonds and leaking of the encapsulated drug before reaching deep skin penetration [42]. there are four key types of liposomal delivery systems—conventional liposomes, sterically-stabilized liposomes, ligand-targeted liposomes, and a combination of the above [44]. Conventional liposomes consist of a lipid bilayer that can be composed of cationic, anionic, or neutral (phospho)lipids and cholesterol, which encloses 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 was 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 [44,45]. 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 demonstrating improving skin penetration and many clinical trial was registered and some of them has been authorized as topically applied medicinal products such as Pevaryl® Lipogel, Maxilene® cream, Lipoxysan®, Supra-vir® cream [46].

4.2. 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 are attached spontaneously [47–49]. 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 Walls forces or other electrostatic interactions [50,51]. 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 [48,52]. In general, liposome could be designed from either natural or synthetic lipids [50].

The utility of liposome as drug couriers 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 to several substances, mostly drug molecules, such as antibiotics, anti-fungal, 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 molecule and metabolizes them instantly. The poor design and characterization also responsible to the problem. Then, strategies are required to against the issues [49,53,54].

To produce high quality liposome, it's necessary to rely on two basic matters, its size and membrane lamellarity [49]. 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 distinguish features among the three type of liposome preparations is 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 [55,56].

4.3. Nanoencapsulation method of liposome as nanocourier

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 permits the delivery of a variety of macromolecules, such as DNA, proteins and imaging agents [44,57].

Nanoencapsulation can be defined as the inclusion of bioactive or the entrapment of natural compounds in carriers that are of nanoscale dimension, this drug delivery approaches used for the enhancement of solubility of many active pharmaceutical ingredients (API), enhanced stability by shielding APIs from the harsh [58]. This modification of phospholipids, preserve to improve self-sealing characteristics in liposome and in aqueous materials, which helps to improve the number of application in various fields including agriculture, food processing, cosmetics, tissue engineering and pharmaceuticals as an encapsulation structure for the modification, protection and targeted delivery of the required bioactive compounds in cancer therapy [59].

Nanocarriers are widely applied in formulation and development due to their numerous advantages in drug delivery such as a powerful approach to enhance bioavailability and solubility, prolong the duration of action, and improve drug stability. Nanoliposome carried encapsulation system can be attained by two other mechanisms which include (1) passive loading encapsulation, which is done by the entrapment of compounds during the process of vesicle formation. Here, hydrophilic compounds are encapsulated within the aqueous phase, while hydrophobic compounds are located in the lipid bilayer of the liposomes. On the other hand, amphiphilic molecules are located in their lipid soluble region between the liposomal lipid bilayers. (2) Active or remote loading encapsulation, involves the entrapment of bioactive compounds into intact vesicles. Bioactive ingredients are inserted in the liposomes with the additional driving force potential achieved by ammonium sulphate (weak base) and calcium acetate (weak acid). This method was found highly effective in the formulation of higher drug or compounds to lipid ratio by the action of pumping or forcing mechanism. In addition, the product should be controlled by ‘‘inside locking of bioactive compounds’’ to the liposome, which would help to enhance the control releasing activity (Fig. 2B) [59–61].

4.4. Liposome as drug delivery for skin disease

Topical administration for antibiotic is the most common route to treat skin diseases caused by bacterial infection. Among other treatment modalities, it’s relatively convenient and less invasive. Antibiotics as topical route could deliver and access many layers of skin tissues efficiently compared to systemic route. For example, local infection due to insect bite will likely to heal faster by applying the antibiotic ointment than the oral one since it provides less side effects as it minimizes sum of drug molecules reach the target tissue. Topical route is also cost efficient [62,63]. However, the increased phenomena of antimicrobial resistance worldwide has threatened the available antibiotics of all classes and actions especially toward Gram-negative bacteria. Sophisticated process could occur to enhance and amplify such bacteria’s ability to defend from antibiotic permeation, especially when it involves the cell membrane system [64,65]. Compared to Gram-positive bacteria, Gram-negative bacteria has two distinct layers of membranes, the outer membrane that consists of thick lipid component called lipopolysaccharide (LPS) and the cytoplasmic cell membrane that rich of peptidoglycan. These two components are particularly strong to block any polar molecules,

yet it tends to be more lipophilic (Fig. 3) [65,66]. Therefore, strategy is required to establish better activity in killing the bacteria and slowing resistance cases. Various vehicles could transport the antibiotic in topical route, such as ointment and gel. Nevertheless, it takes years to develop high and sustainable drug formulation [52]. Many scientist elicit some ideas by combining various available natural-derived compounds to the antibiotics. Lipid based drug vehicles such as liposome are preferable in terms of ability to penetrate further into bacteria cytoplasm [67]. Problems with hydrophilic drug molecule is the notably positive charge, thus it inhibits further bond with the bacteria outer membrane. The size of bacteria cell membrane in which mostly arranged by lipid structures is vary in size depending on its chemical classes. Gram-positive bacteria has relatively thicker cell wall (20-80 nm) compared to Gram-negative bacteria (<10 nm) [68,69]. Although the outer membrane of Gram-negative bacteria is highly non-polar for its rich lipoprotein component (~70%), it still enable tiny molecule of amino acid and sugar to permeate through specific canals, called porins [70]. As well as bacteria characteristics, liposome possess basic similarity in which it also contains two different layer of lipid thus it increases ability to fuse together [71].

To obtain efficient permeation through skin barrier, the most crucial factor is to determine the current size of the drug molecule as well as its courier. Drug courier with approximately more than 300 nm in diameter size will most likely difficult to permeate through skin pores [72]. Liposome has variety of size, 25-50 nm in diameter called as small, unilamellar vesicles (SUVs), 50-500 nm in diameter called large, unilamellar vesicles (LUVs) and 500-10.000 nm in diameter called large multilamellar vesicles (LMVs). To reach maximum capacity, liposome needs to be designed as smaller as possible. Thus, LUVs are mostly preferred compared to other size forms. LUV enhance the penetration system of liposome since it contains phosphatidyl ethanolamine which it can be fused together with skin lipid easily (Fig. 4) [73]. Cholesterol is usually provided to ensure liposome stability. With its unique physiochemical characteristic, it is important to assess whether each of loaded drug molecules are well capsulated. Various specific drug-trapping methods are reported, however each drug may create different result. The main principal to obtain successful preparation is to elicit drug's solubility and to find a perfect homogenous compound. Theoretically, lipophilic drug molecules may retain inside the lipid bilayer compartment of the liposome while hydrophilic one will easily blend during aqueous phase [74]. Aside the liposome

flexibility in size, notable goal to achieve for topical drug delivery is limiting the allergic reactions upon the compounds. Skin irritation usually emerges from chemical substances, such as surfactants. Lipid-based material will carry fewer side effects in terms of induce local immunity system. One study from Wu, et al. (2022) has tested licorize flavonoid, Licochalcone A, loaded with skin keratine liposome (LAL) for its wide range of benefits to guinea pig skin. Skin irritation test showed no visible signs of local inflammation from the substances applied on its hairless skin during three different observation period. Further analysis is taken to provide area distribution of the loaded substances inside the skin tissue. Fluorescence activity emits high intensity signal for LAL compared to non-liposome group [75].

Understanding basic pharmacokinetic of certain antibiotic especially when it is in topical route is as important as finding the suitable delivery materials. Fluoroquinolones and aminoglycoside are considered to be concentration-dependent type of antibiotic which means to eradicate targeted bacteria, it needs to reach its peak concentration. The problem of dosage usually appears in linear with the toxic effects. Bigger dosage means bigger side effects. The strategy is always to gain maximum pharmacology benefits and to decrease the dosage volume. Incorporating the antibiotics with liposome is possible especially in nanosized. β-lactams are class of antibiotic that mostly time-dependent. To carry its full bactericide activity, once it's administrated, it takes frequent release to systemic. Thus, time is very crucial in repeating the required amount of drugs concentration. However, maintaining such stable concentration in plasma needs consistent environment. Human body complexity deliver sophisticated environment and it may alter according to specific condition. Therefore, antibiotic concentration could increase and decrease with the flow of time. Serious action is needed to solve the problem. Compactible courier, such as liposome, may provide more stable and stronger phagocytic activity to omit better effect [76,77]. The problem regarding topical route focus in permeation system. Inefficient and inappropriate antibiotic concentration in plasma increase the risk of resistance. Meanwhile, novel antibiotic discovery takes years to conduct and the mortality trend number keeps increasing annually. Unlike any conventional drug delivery materials, liposome allows for nanoparticle formulation and robust combination methods with various compounds, such as polymer and other non-organic material (e.g. silver, gold, etc). Sang et al. (2022) loaded Polymyxin B (PMB) into modified liposomal system (P-

lipo) and observed higher concentration to cross into Pseudomonas aeruginosa as liposome size permits better penetration into the bacteria cytoplasm by engaging with membrane-anchoring lipid A on the outer wall membrane. In vivo test revealed coherent result. Group of mice injected with D-galactosamine hydrochloride to induce shock septicemia showed significant survival rate up to 60% when given P-lipo compared to non-liposome loaded group. In conclusion, P-lipo appeared to exhibit greater ability especially it enables bacteria lipopolysaccharide (LPS) binding [78].

4.5. Liposome's ability in enhancing antibiotics permeation across skin barrier

To design particular drug molecules for gaining more benefits than the harm is totally a real challenge. As the number of antibiotic resistances increases each day, more research is pushed forward to stop this inevitable event. Skin infections caused by bacterial pathogens such as skin normal flora, Staphylococcus aureus (*S. aureus*), contributes to specific antibiotic-resistant called methicillin-resistant *S. aureus* (MRSA). The number of MRSA cases continue to spread dangerously every single year throughout countries, as reported by CDC. More than 70.000 severe infections and nearly over 9000 deaths per year are counted at least [79,80]. The basic characteristic of MRSA is the ability to resist for most beta-lactam antibiotics such as flucloxacillin, methicillin, oxacillin and cefoxitin. The bacteria is commonly found inside the skin pus from diabetic foot ulcer or chronic impetigo. However, the drug-of-choice for such case is Vancomycin in which in many low and middle income countries, the use of the antibiotic is limited and quite inaccessible [81,82]. Unfortunately, more and more Vancomycin resistant *S. aureus* infections are lined up to the surface for the last two decades with at least 11 *van* gene clusters that contributes 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) [83]. New breakthrough in drug delivery system allows various antibiotics to combine in one courier, from drug to drug from different antibiotic class and even to drug to natural substances. With the growing number of plausible occurrence as part of pathogens adaptability and durability against antibiotic, more strategies are required to diminish the potential harm, such as designing a better vehicle for the antibiotics [79,84][85].

Large demand of research in liposome as part of futuristic courier for drug molecules also enable high quantity and quality of improvement in medicine. In dermatology, the usage of liposome has been genuinely applied for various type of drug formula, such as ointment and gels. However, to keep the stability in supporting the ability to penetrate further layers of skin barrier become focus issue. Nanopharmaceuticals help to improve the current problem by manipulating the liposome profile chemically [86,87]. Liposome is vast of lipid content, thus it could reach down even deeper of the skin barrier to tissues in which it is all lipid bilayer. Coating specific antibiotic with liposome increases the solubility and promisingly more beneficial to be transported through skin with its negatively charged condition. When it is designed with more positive charged, the visible effect could exert multiple times (Fig. 5) [88,89].

Compared to antibiotic alone, liposome could enhance the antibiotic ability to permeate through infection sites [76,77]. Cytotoxic activity of chloramphenicol-loaded DA (deoxycholic acid) liposome showed twice amount of deposition of chloramphenicol concentration in follicular level of nude mouse' skin compared to aqueous control group. The reported precise drug concentration when it's loaded with DA liposome inside the stratum corneum of the mouse is 5.8 μg/cm^2 while the chloramphenicol alone is 4,6 μg/cm^2 [90]. More importantly, better result is shown when the liposome is designed in nanosized. A study to observe the nanosized Rifampicin's ability against *S. aureus* showed greater bacterial colony reduction (in CFU) than the other group which treated with Rifampicin alone at fifth day observation. Enhancing the Rifampicine by adding cationic lipid such as monoolein (MO) and N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate (DOTAP) (NanoRIF) had higher cytotoxic activity toward the *S. aureus*. Mice treated with 25 mg/kg NanoRIF had significant lower or no detectable bacteria ($p<0.05$) compared to untreated group. However, the average reduction was deliberately better in 12,5 mg/kg group [67]. Another strategy is required to enhance the outburst activity specifically as sustained mode of certain drug from liposome courier, namely fuse altogether with water-based gel. Compared to Chlorhexidine alone, liposome-in-hydrogel formulation gives better result in increasing membrane active antimicrobial activity [91]. Other study suggests when vancomycin is loaded with liposome, phagocytic ability of cultured leukocytes toward the *Streptococcus aureus* significantly improves. To corelate the whole studies, topical nanoliposome is much preferred

as it will likely to be recognized well by bacteria cell wall through endosomal mechanism and provide less interaction with natural biofluid [92].

6. Current research : in vitro and in vivo

5.1. Daptomycin

Although *S. aureus* is considered as part of microbiome that inhabits human skin, many infection skin diseases are mainly caused by the bacteria. The degree of clinical manifestation from the pathogen's infiltration is varied according to level of immunity. Several antibiotics especially topical one provides great benefit to against such bacteria, however redundant application and irrational antibiotic consumption always leads to longer healing process from the infection. Daptomycin is a novel cyclic lipopeptide antibiotic derived from type of fungi called *Streptomyces roseosporus* with strong ability to kill most of Gram-positive pathogens including MRSA and vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant Enterococci (VRE), glycopeptide-resistant *S. aureus* (GRSA), coagulase negative *Staphylococcus* (CoNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP), *Clostridiodes difficile*, *Clostridium perfringens*, *Finegoldia magna, Bacillus megaterium,* and *Propionibacterium acnes* [93,94].

One study showed how daptomycin-loaded flexible liposome by using diffusion cell method against *S. aureus* until the visible biofilm is formed. The ratio of cell viability of control to experimental group is reported nearly $1:10^8$. Further study is conducted with in vivo experiment with control vs daptomycin-loaded flexible liposome group mice is performed. Within 4 days after regular daptomycin application to the hairless part of the mice' skin, scattered and less visible *S. aureus* biofilm could be seen from the scanning electron microscope. However, the similar result is also given from the positive control group which is the intravenous antibiotic injection [95].

5.2. Tetracycline

Acne vulgaris (AV) is a major skin disease that mostly occurs during puberty. Alongside various infection skin disease such as pyoderma, AV could develop tremendous manifestation starting from blackhead to excessive pustules. The well-known pathogens involved in AV are *Propionibacterium acnes*. The wide range of clinical appearance in AV requires different medications. Topical antibiotic is one of the most applied medicine to treat

such disease. Tetracycline family is considered to generate great magnitude of bactericidal activity and acts by inhibiting bacteria' protein synthesis process [96,97]. Specifically, tetracycline could disable the chemotaxis mechanism of neutrophils induced by *Propionibacterium acnes*, reduce IL-8 expression and phospholipase A2 to reactive oxygen species production [98].

Eroğlu et al. (2019) reports in one study using tetracycline HCl and tretinoin loaded hydrogel liposome on *S. aureus* and *S. epidermidis* give significant reduction in bacteria life growth. The MIC between non-hydrogel and hydrogel preparations slightly different with non-hydrogel appear to show smaller MIC than the hydrogel one [99].

5.3. Rifampicin

Skin has myriad function especially in giving protective barrier for deeper parts of human body. Tissue discontinuity of skin due to trauma or non-traumatic cause may affect the integrity of immunity alertness toward various external threats such as pathogens infiltration. Rifampicin has been acknowledged to provide extensive benefits in fighting against many spectrums of bacteria by targeting the RNA synthesis of bacteria. In detail, Rifampicin molecules bind to the active site of RNA polymerase thus inhibit the RNA elongation [100]. Rifampicin has been used to treat patients with chronic wound healing that manifest as progressive infection skin disease such as diabetic ulcer complication. However, to gain stable topical form of such antibiotic requires further studies especially in finding suitable drug delivery. Wallenwein et al. (2023) conducts study to encapsulate Rifampicin with nanoliposome under oxidative stress model. Damaged wound or slower rate of healing process shall correlate with the oxidative process. When compared with ascorbic acid, Rifampicin loaded liposome deliver similar activity in reducing the level of oxidation and save the Rifampicin from lysosomal degradation. Also, as more oxidation products are released, more Rifampicin molecules are bursting out from the liposome vesicles [101]. Another study observed the ability of Rifampicin-loaded to liposome exhibits bigger ability to kill *Mycobacterium abscessus* compared to group with no liposome encapsulating the antibiotic [102].

5.4. Amphotericin B

Cutaneous leishmaniasis (CL) is a common type of leishmaniasis disease that affects almost 700.000 to 1 million people every year. The main cause of such disease is protozoan

parasite *Leishmania* from *Trypanosomatidae* family. This vector borne disease usually creates skin ulcers. Amphotericin B is second line antibiotic for Leishmaniasis with specific activity to induce leakage throughout the protozoa's membrane cells [103]. To provide greater effect against Leishmania protozoa, topical route is the most convenient and less-toxic route of administration. In addition, smaller size will be preferable for skin topical drugs. Jaafari et al. (2019) studies the ability of Amphotericin B loaded liposome (Lip-AmB) to kill the Leishmania major protozoa which infecting cultured macrophage. It is reported that the experimental group shows non-inferiority ability to suppress the protozoa viability compared to Fungizone© as positive control. However, significant appearance is shown through in vivo study. After 8 to 12 week of Lip-AmB 0,4% exposure, parasitic count inside the mice spleen is much lower than the placebo group ($p<0,001$) [104].

5.5 Azithromycin

One of the largest populations amongst skin microbiomes is *S. aureus*. Almost 76% of various skin infection disease could occur from such bacteria, especially pyoderma. Not only that, diabetic ulcer condition could be worsened if the bacteria infiltrates further into skin tissue layers. *S. aureus* colonization is found mainly on superficial layer of skin and adheres with corneocytes. Although it often causes pyogenic skin lesion, *S. aureus* has also been acknowledged as one of the causes in atopic dermatitis (AD) [105,106]. Azithromycin is antibiotic from macrolide class that inhibit bacteria growing by disrupting its protein synthesis through binding with near site of peptidyl transferase center on 23S rRNA [107]. Pathogenic bacteria are the most targeted bacteria type of this antibiotic. However, MRSA cases has growth concerns to many clinicians worldwide for inevitable cost-consumed effects. It contributes to community acquired nosocomial infection and further morbidity to mortality caused by multi-drug resistant (MDR). Many reported studies claimed due to azithromycin poor solubility in water makes the antibiotic is difficult to find effective and efficient courier. Microemulsion is one of the strategies to enable azithromycin penetrates better through skin tissue [108,109]. Another strategy is to load the antibiotic with liposome. Rukavina et al. (2018) studied the effect of azithromycin-loaded liposome to treat MRSA infection and examined the permeation power into porcine ear skin. Approximately 90% of bacteria growth could be inhibited by given the azithromycin-loaded liposome at 0.5 to 8 µg/ml while the free azithromycin could exhibit such activity at bigger dose range, 8 to 32 µg/ml. The main goal

for any topical drug is to reach maximum concentration in local site. Thus, restricting undesired azithromycin penetration deeper than superficial tissue layer should be achieved. The experiment showed the entrapped antibiotic with cationic liposome (CATL) optimized the drug concentration in stratum corneum about 35% while the free azithromycin concentrate higher in deeper skin layer [88].

7. Conclusion

Bacteria physical features that mostly contains basic macromolecules such as lipid, protein and glycans. Antimicrobial agents are designed to target various important part to bacteria's machinery system and disrupt them by accessing specific ligands or receptors out or in side of the bacteria cell. However, rising cases of bacteria survival rates and irrational prescribing antimicrobial lead to higher prevalence rate of antimicrobial resistance. To ensure full eradication of bacteria colonies that resides in human body, many parameters are needed to achieve. Inappropriate dosage regiment, delayed medicine taken, and abnormal health condition may change the normal pharmacokinetics of the antimicrobial agents. For example, lesser plasma concentration compared to bacteria MIC may lead to further resistance cases. Up until now, scientists believe the known challenge regarding antimicrobial resistance is inevitable. Therefore, breakthroughs are required to give solutions in the future [110–112]. Futuristic drug delivery system has started to become popular recently. Liposome enables higher drug molecule loading intracellular due to its adaptability to be designed in nanosized. With high components of phospholipid part, tissue with lipid bilayer system is easily to be permeated. Also, liposome could be generated with many other organic and even non-organic molecule such as silver, gold, magnets, etc. Efficient and appropriate internalized drug concentration are the basic purpose for maintaining better effect, in this case is to kill the pathogenic bacteria. Clinically, many liposome based drug has been approved by FDA (Food and Drug Administration), although mostly still limited on systemic to transdermal apply. Topical liposome drug delivery especially for antibiotics are not well popular enough since studies probably still on-going. Yet, topical application is relatively non-invasive, convenient and effective for treating skin infection disease. Wide and irresponsible usage of this type of delivery system appears to increase the existing cases of antibiotic resistance. A few studies also indicate that no significant difference between applying post-surgical topical antibiotic

alone and non-antibiotic post-surgical infection prevention agent such as paraffin or petrolatum. Although to manage efficient drug molecule absorption is quite complex pharmacokinetic study, the main principal required is to ensure the as smallest dosage as possible, or in other way is to choose minimum therapeutic dosage [17,28,113,114].

In conclusion, liposome ability to enhance permeation system of antimicrobial drug for topical application could provide further potential for future breakthrough in combating antibiotic resistance. More studies are required to strengthen the findings and continued with clinical setting research.

Conflict of Interest

The authors declare no competing interest either in financial or interest during the overall making of the paper

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40 Figure and Table legends Fig. 1. Skin histology 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) consist of aqueous area that is important for most hydrophilic drug molecules to be kept inside the core. (A)

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41 (B) 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. (A)

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42 (B) Fig. 4. Three different type of liposome according to its molecule size Fig. 5. Entrapment ability of liposome to coat various drug molecule increase the bioavailable of drug and further enables higher plasma concentration with as smallest dosage given as possible.

43 Table 1. Various formulation of antibiotics for skin, ear and eyes infection disease No. Drug Action Formulation Target 1 Mupirocin Inhibiting bacterian isoleucyl-tRNA enzym causing leads RNA and protein synthesis. [115] 2% Cream/ Ointment Epidermal skin 2 Fucid Acid Interfering synthesis bacterian protein and translocation factor G of ribosome 2% Cream/ Ointment Epidermal skin 3 Neomycin Inhibiting proterin becterian synthesis by binding 30S subunit of bacterial ribosome 0,5% Cream Epidermal skin 4 Tetracycline 16s rRNA binding and overlaping tRNA in 30s 3% Solution/ cream Epidermal skin

		subunit cause bacteri replication		
5	Silver Sulfadiazine	Bacterisidal effect by cellular protein and membran cell cause inhibiting synthesisi of folic acid	1% Cream	Epidermal skin
6	Mafenide Acetate	Excellent penetration	8,5 % Cream/ 5% Aqueous Solution	Epidermal skin
7	Chloramphenicol	Anti hypersensivitiy	5%, 10% Drops	Outer ears cannal
8	Ciprofloxacin	Good for tympanostomy tube	0,3% Solution	Outer ears cannal
9	Azitrhomycin	Poor corneal	2% Cream/ Ointment	Anterior eye segment
10	Gentamicin	Excellent penetration in cornea, acting: binding 30S ribosomal in bacteri and ceasing protein on pathogenic bakterian.	500 unit/g Ointment	Anterior eye segment
11	Ciprofloxacin	Good penetration	0,5% Cream	Anterior eye segment
12	Chloramphenicol	Good corneal	3% Solution/ cream	Anterior eye segment