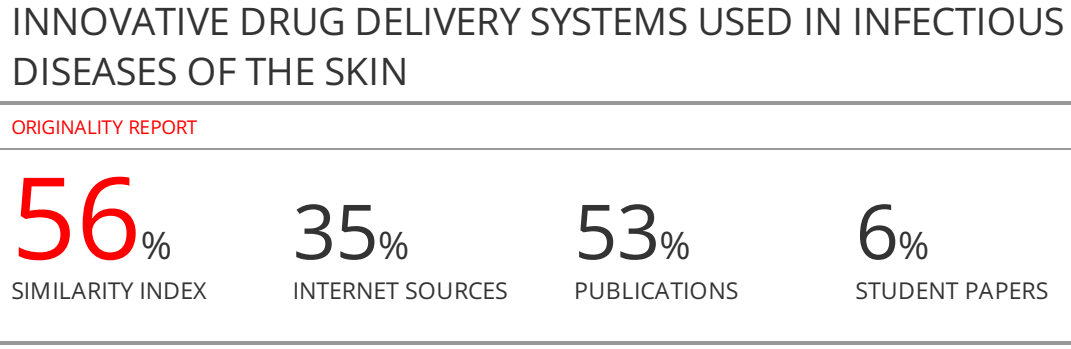
**Reviewer’s Comments**

**INNOVATIVE DRUG DELIVERY SYSTEMS USED IN INFECTIOUS DISEASES OF THE SKIN**

# ABSTRACT

The skin is the organ that is most exposed to microorganisms in our body. Skin infections are usually caused by bacteria, fungi and viruses. The low penetration of the conventional systems used in infectious diseases of the skin through the stratum corneum causes low bioavailability. For this reason, nano-sized drug delivery systems that can be used in infectious diseases of the skin are currently being investigated. In this review, innovative studies carried out over the years are presented. New topical formulations such as nanoparticles, microemulsions, liposomes, nanofibers, micelles are among the most researched drug delivery systems.

Studies have shown that the small size and controlled release of these delivery systems provide more effective treatment by increasing the penetration of the drug into the skin. It has been found that drug delivery systems provide better antibacterial effect, especially in resistant infections caused by MRSA. At the same time, the effects of the use of drugs used in traditional treatment with these carrier systems were investigated. As a result, nano-sized carriers have a very important place in the treatment of infectious diseases of the skin.

**Key Words:** Skin infectious diseases,topical, drug delivery systems, modified release dosage forms

**INTRODUCTION**

In line with the different cell types it has, the skin basically forms a three-layered structure: epidermis, dermis and hypodermis1. The *stratum corneum* (SC), which has an important position in the structure of the skin, is a lipid structured layer containing multiple corneocyte layers in the epidermis2. The drug is absorbed through the skin via the SC. SC acts as a barrier in the transdermal delivery of drugs3. Conventional formulations such as gels and creams show poor penetration while passing through the SC. For this reason, it is necessary to develop innovative drug delivery systems4. Innovative drug delivery systems, being nano-sized, penetrate the skin better and increase absorption. By providing localized drug accumulation, it prolongs the residence time of the drug in the skin. It reduces the side effects of the drug by limiting the systemic absorption. It also allows for controlled drug release5. The skin is an organ open to microorganisms, and bacteria, fungi and viruses are among the pathogens that cause skin infections6,7. Due to the limited success of conventional dosage forms in skin infections, intensive studies are carried out on innovative drug delivery systems including microemulsions, liposomes, nanoparticles, nanofibers and micelles8,9. In this review, studies on infectious diseases of the skin and dosage forms containing innovative drug delivery systems for use in the treatment of these diseases are presented with an overview.

**INFECTIOUS DISEASES OCCURING ON THE SKIN**

**Bacterial Diseases of the Skin**

Infections with *Staphylococcus* and *Streptococcus* species are the most common skin and soft tissue infections. In clinical practice, infectious impetigo, erysipelas, panniculitis, and furuncles are the most common diseases10. Necrotizing skin and soft tissue infections include a series of infections known as skin, subcutaneous tissue and superficial fascia infections, which are characterized by the development of necrosis in these structures11.

Of these, impetigo is characterized by a superficial, non-purulent, pruritic, vesicular rash that turns into pustules on the face or extremities, followed by golden, honey-colored crusts 11. Impetigo accounts for 50% to 60% of all bacterial skin infections. Non-bullous impetigo typically begins as a single red maculopapular lesion that quickly becomes a vesicle. The vesicle may rupture, and the contents may dry out to form characteristic honey-colored crusts. It is caused by *Staphylococcus aureus*, group A beta-hemolytic *Streptococcus pyogenes* or less commonly anaerobic bacteria12.

Ecthyma gangrenosum refers to the sepsis state of *P. aeruginosa*. Clinically, it is characterized by the rapid development of a localized lesion, initially vesiculobullous or papulonodular, on an erythematous, edematous background that transforms into local signs of skin necrosis and an ulceronecrotic lesion within 12-24 hours. Lesions are usually few in number, but they may be in multiple and different evolutionary stages13.

Acute bacterial folliculitis involves infection of one or more hair follicles. It is the most common form of superficial folliculitis. It is 'Impetigo of Bockhart' and is caused by *S. aureus*. Recurrent folliculitis is usually due to community-acquired methicillin-resistant *S. aureus* (MRSA). Deeper folliculitis may be chronic and associated with shaving of hairy areas11.

An abscess is a collection of pus within body tissue11. In 25% of the cases, *S. aureus* may be the only factor14. It is typically deeper and more painful than folliculitis. If the affected area is easily accessible and there is no cellulite on it, drainage is an adequate treatment11.

Cellulite is a disease with an orange peel appearance, which occurs as a result of superficial skin edema surrounding the hair follicles14. It is a deeper and borderline disease that can invade lymph tissue and blood. Treatment should be directed towards typical gram-positive pathogens, particularly streptococci11.

Erysipelas is a more superficial form of cellulite. Erysipelas is more common in older age. It is typically caused by group A streptococci, but group C and G streptococci can also cause this disease11.

Necrotizing fasciitis is a serious picture in which the infection starts with changes such as erythema on the skin surface and extends to the fascia layer14. The disease caused by the synergistic association of aerobic or anaerobic bacteria is defined as type I. Type II necrotizing fasciitis, which is monomicrobial, is also called “streptococcal gangrenous cellulitis”13. *Streptococcus pyogenes* is the most common pathogen. This is followed by other β-hemolytic streptococci such as newly emerging *Streptococcus dysgalactiae*. MRSA, *Clostridium spp*., *Vibrio vulnicifus*, and *S. aureus*, including other gram-negative bacilli, are rare causes of type II infection15.

Fournier's gangrene is considered a variant of necrotizing fasciitis with an initial and specific location in the genital or perianal region. It runs in the superficial and deep planes of the urogenital and anogenital fascia. The most common infectious agent is *Escherichia coli*13.

**Viral Diseases of the Skin**

Human papillomavirus (HPV) and herpes simplex virus (HSV) are two common viral venereal diseases. HPV infections are characterized by anogenital warts and less frequently premalignant or malignant lesions. HSV infections classically present as grouped vesicles on an erythematous base and are accompanied by burning or pain16.

Condylomata acuminata are warts that appear in the anogenital area as a result of sexually transmitted HPV. Condylomata acuminata is present in the anogenital region as single or multiple flat, papillae, hyperpigmented, pink or tan, well-circumscribed papules or plaques16.

Anogenital herpes is an infection of the external genitalia and anus with HSV type 1 or type 2 that classically presents as grouped vesicles on an erythematous base. Similar to HPV, HSV is transmitted by skin contact or contact with vesicular fluid16.

Common warts (Verruca vulgaris) are clinically characterized by exophytic papules with a rough, papillomatous surface. The most affected areas are the hands and fingers. In addition, stalked and filiform lesions can be seen, especially in the periorificial face areas. In dermoscopic examination, vascular papillomatous areas with thrombosis can be seen in each papilla center17.

Flat Warts (Verruca plana) are characterized by the presence of normochromic pinkish or brown papules with a flat, smooth surface. They are most seen on the back of the hands, upper extremities, or face. Dermoscopy reveals evenly distributed punctate or globular vessels on a yellowish-brown background17.

Palmoplantar warts are endophytic, hyperkeratotic, and often painful lesions. When they occur more superficially with lesions that coalesce into large plaques, they are called mosaic warts or mirmecia17.

Molluscum contagiosum is a skin infection caused by the molluscum contagiosum virus from the poxvirus family. Atypical presentations such as solitary or giant lesions mimicking warts and epidermal cysts may also be seen. It often shows a white-yellowish polylobularstructure, and a central pore or navel surrounded by crown-shaped peripheral vessels. Transmission occurs through direct contact with infected skin17.

Eruptive pseudoangiomatosis is a self-limiting condition characterized by the appearance of erythematous papules with a halo of vasoconstriction. Lesions are presumed to be triggered by insect bites or viral conditions, including echovirus, Epstein-Barr virus, or cytomegalovirus17.

**Fungal Diseases of the Skin**

While most fungal infections are superficial, some types of fungi can cause life-threatening infections18. Fungal diseases are extremely common, and it is estimated that around one billion people worldwide suffer from dermatomycosis or other fungal infections of the skin, hair and nails. The prevalence and incidence of dermatomycoses vary according to socioeconomic and geographical conditions. For example, while dermatophytes thrive in hot and humid climates, dermatomycoses are more common in tropical countries 19. Superficial fungal infections of the skin, hair and nails are mostly caused by dermatophytes, *Candida spp*. and *Malassezia spp*., as well as dimorphic fungi such as *Sporothrixschenckii* can also cause infections in endemic areas20.

Dermatophytes are a group of keratinophilic filamentous fungi that cause superficial infections in keratinized tissues and affect 20-25% of the world's population. They are known to invade the SC, causing onychomycosis, tinea cruris, tinea corporis, and tinea capitis. *T. rubrum* is the most common pathogen causing dermatophytosis, and the emerging dominance of the *T. mentagrophytes* complex has also been noted recently21.

Onychomycosis represents 50% of all nail diseases with a worldwide prevalence ranging from 2% to 8%. It can be caused by different species: dermatophyte fungi, non-dermatophyte fungi and leveduriform fungi. About 90% of all hallux onychomycosis are caused by dermatophytes. The clinical aspects of onychomycosis are mainly onycholysis, changes in nail color and subungual hyperkeratosis17.

Tinea capitis is an infection characterized by presenting a single plaque, which can be of microsporic type, caused by dermatophyte fungi that affect the scalp and hair follicles. Trichosporon type transmitted by human-to-human contact, usually showing multiple lesions; The favus type or Kerion celsi type is an inflammatory form with the presence of pustules and micro-abscesses. Clinically, areas of hair loss are observed with toned hair shafts associated with the presence of scaling, inflammation, and pustules17.

Tinea nigra is a superficial mycosis caused by the dematiaea fungus Hortaeawerneckii that occurs predominantly in tropical and subtropical climates. Clinically, it presents as an irregularly pigmented brownish or blackish macula that classically occurs on the palms and soles17.

Mucormycosis has become the third life-threatening fungal infection worldwide, after candidiasis and aspergillosis. According to clinical findings, it is divided into cutaneous and soft tissue, rhino-orbito-cerebral, gastrointestinal, renal, abdominal, bones and joints mucormycosis. Abscess, necrosis, dry ulcers, skin swelling and eschars are characteristic signs21.

Candidiasis, (*Candida spp*.) is a commensal organism of human skin that can go into pathogenic mode to cause mucosal or disseminated candidiasis. It is a unique type of candidiasis characterized by severe, recurrent or persistent infections of the skin, nails and mucosa by Candida organisms21.

Malassezia is the most common fungus on mammalian skin and >90% of all skin fungi belong to this genus. Malassezia has the potential to invade SC and interact with the host immune system, either directly or through chemical mediators. Therefore, Malassezia can be associated with a variety of skin disorders, from chronic to severe. It is estimated to affect more than 140 million people worldwide each year21.

Sporotrichosis is a skin infection caused by the fungus Sporothrixschenckii and its transmission is usually by direct inoculation into the skin and subcutaneous tissue. The most common cutaneous manifestation is lymphocutaneous, where verrucous papules or nodules develop at the site of inoculation with further spread following the lymphatic pathways17.

Chromomycosis, also known as chromoblastomycosis, is a chronic fungal infection most caused by traumatic inoculation of dermatozoa fungi of the genus *Fonsecaea*or *Cladophialophora*. In chromomycosis, dermoscopy reveals a pinkish-white background, yellow-orange oval structures, polymorphic vessels, scaling and crusting17.

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans*, which is more common in immunocompromised patients. Skin manifestations are usually due to systemic dissemination, but they may rarely occur with direct inoculation. There is a wide range of clinical manifestations, but the most common are papules with pearly white cores17.

Eumycetoma or mycetoma is a chronic fungal infection that affects the skin and subcutaneous tissue. Several species of hyaline and dematiaceous fungi may be causative pathogens; but the main ones are *Madurellamycetomatis*, *Nigrogranamackinnonii*, *Trematosphaeria grisea*, *Falciformispora senegalensis*, *Scedosporiumapiospermum* and *Acremonium falciforme*. Infection typically occurs by inoculation and affects the distal parts of the lower extremities. It is characterized by the formation of a tumor area, fistula tracts and macroscopic granules. Depending on the fungus involved, the granules may be black or yellowish-white17.

Histoplasmosis is an infection caused by inhalation of the fungus histoplasma capsulatum. Most infections are asymptomatic or self-limited, but some individuals may have serious or widespread conditions. Skin lesions occur in disseminated histoplasmosis and have a wide range of clinical presentations17.

Blastomycosis is an infection caused by inhalation of the fungus blastomyces dermatitidis, which can cause an asymptomatic condition or pulmonary and extrapulmonary manifestations that are endemic in parts of North America. The skin is the second most affected organ, after the lung and usually after hematogenous spread, but rarely traumatic grafting may also occur17.

Talaromycosis, talaromycesmarneffei, is an important thermal dimorphic fungus in tropical countries of South and Southeast Asia. The characteristic lesions are papules with central necrosis, but other symptoms may also occur, including papules and ulcers21.

**Parasitic Diseases of the Skin**

Epidermal parasitic skin diseases include scabies, pediculosis, cutaneous larva migrans, myiasis, and tungiasis22. Pediculosis is an infestation of lice on the body, head or groin area. Lice are ectoparasites of the order Phthiraptera that feed on the blood of infested hosts. Of the thousands of lice species, only Pediculus humanus and Phthirus pubis (pubic lice) need humans as hosts. Pediculus humanus contains 2 morphotypes: P.humanus corporis (body) and P humanus capitis (head) louse. They live on clothes and attach to nearby skin to eat blood. Females lay eggs at the seams of clothing. In suitable environments, the eggs develop into nymphs after 6 to 10 days, which mature into adults that live 1 to 3 months. Lice leave their hosts and die within 3 to 5 days. Patients with body lice infestation present with generalized itching and diffuse lesions on the neck, shoulders, upper back, flanks, and waist23.

Head lice are obligate human parasites that spend their entire life cycle on the scalp and feed on blood every few hours. Female lice live ≤30 days and lay about 10 eggs per day. Itching, papular urticaria, excoriations, and cervical/occipital lymphadenopathy may occur. Diagnosis is made by direct observation of lice or nits on hair shafts. Head lice can carry and transmit Staphylococcus aureus and Streptococcus pyogenes23.

Tungiasis is an ectoparasitic disease caused by the skin of the female Tunga penetrans or, less commonly, Tunga trimamillata flea. Lesions predominantly affect the feet. Typically, after a painless introduction to the feet, embedded fleas mature after a few weeks. The early-stage lesion is a 1 mm red-brown macula that transforms into a central dark punctal nodule. Flea blockage after egg production causes swelling, erythema, itching and pain. Eventually, egg release and parasite death trigger severe inflammation, leading to a black crusted papule that heals with a punctured scar. The penetration site is ≤500 μm in diameter, and therefore secondary bacterial infections, including cellulitis, necrotizing skin and soft tissue infection, frequently occur23.

Scabies is a disease caused by sarcoptesscabiei, an obligate microscopic parasitic mite that lives in the human epidermis, where female mites enter the SC and cause a cutaneous hypersensitivity reaction to its products. In classical scabies, prolonged skin-to-skin contact, including sexual contact, is the primary mode of transmission, and fomite-mediated transmission is rare. It presents with classic morphology of scabies, pruritus, and multiple skin lesions involving finger webs, hands, volar surfaces of wrists, armpits, buttocks, areola in women, and genitals in men. Crusted scabies is most commonly seen in immunocompromised patients, which manifests as hyperkeratosis with or without pruritus24.

Cutaneous larva migrans (CLM), also called creeping eruption, is a parasitic infestation produced by burrowing the larva of Ancylostomabraziliense. The larva enters intact or eroded skin after contact with fecal-contaminated soil. Solitary tracts involving the feet, hands, hips, and genitals are frequently encountered25.

Myiasis is the infestation of the larvae of dipterous (biwinged) flies of vertebrates, including humans. It is traditionally classified according to the site of invasion (cutaneous myiasis, nasopharyngeal myiasis, ocular myiasis, auditory myiasis, urogenital myiasis, and intestinal myiasis). The most common form of cutaneous myiasis is the furncular. Depending on the migratory, invading larva type, myiasis is mainly characterized by Dermatobia hominis (Botfly) and Cordylobiaanthropophaga (Tumbu fly). It is characterized by small, itchy and/or painful boil-like papules or nodules26.

**TOPICAL DRUG CARRIER SYSTEMS**

The impact of skin morphology between body sites and individuals is to determine which drug candidates can be absorbed through the skin, how quickly, and if potent enough, they can be useful in topical products. Only small (molecular weight <500 Daltons), soluble (usually low melting point) and moderately lipophilic (logP value between 0-5) compounds with few hydrogen bonds easily pass SC unless some form of skin penetration enhancement technology is used. A larger and more lipophilic drug has more difficulty in passing into the more hydrated living epidermis due to its poor water solubility27.

To increase the passage of drugs through the SC, they must be inert, non-allergic, non-irritating, cosmetically acceptable, and allow adequate release of the drug into the skin. Many substances act by blocking transcutaneous water loss, forming an occlusive film, and moisturizing the skin to facilitate drug absorption through the skin. Surfactants and aqueous or hydroalcoholic solvents also temporarily disrupt skin lipids, helping the drug dissolve and absorb4. Penetration enhancers are substances that promote drug flow through the skin by interacting with skin components. Penetration enhancers act through a variety of mechanisms. Denaturation or modification of intracellular keratin affects the desmosome and changes the solvent nature of SC by changing the intercellular lipid domain. They push the drug into the skin by increasing the thermodynamic activity in the formulation. They absorb the drug into the skin by penetrating the skin and increasing its solubility in the skin. Numerous compounds such as sulfoxides, alcohols, esters, pyrrolidones, glycols, glycol ether, surfactants and terpenes can be used as penetration enhancers. However, penetration enhancers are often present in the formulation in high concentrations that can cause irritation and immunogenicity. New drug delivery systems have become very interesting recently as they can improve the topical absorption of drugs. They offer advantages such as increased drug accumulation in the target area, minimization of drug degradation, and increased penetration of the drug through the skin4.

The advantages of topical innovative drug delivery systems are summarized in Table 1.

**Table 1:** Advantages of topical innovative drug delivery systems59,28.

|  |  |
| --- | --- |
| **TopicalInnovativeDrug Carrier Systems** | **Advantages** |
| Nanoemulsions | Since they have submicronparticle size, they can easily penetratethroughthe skin pores and reachthe systemic circulation. Transdermal application of both hydrophilicandlipophilic drugs is suitablebecause they containoilsandsurfactants in theirformulations. |
| Solid Lipid Nanoparticles | Itcreates a homogeneousanduniformlayer on the SC andchangesthebarrierpropertiesbyinteractingwiththe skin layers. It has thepotentialtoincrease skin penetrationand skin residence time. |
| Nanostructured Lipid Carriers | Lipid nanoparticles can interactwith lipid bilayermembranesandimprovethepenetration of encapsulateddrugmolecules. |
| Liposomes | It has manyadvantagessuch as controlleddrugrelease, localizeddrugaccumulation in skin layers, reducedsystemicabsorptionandfewerdrugsideeffects. Anotheradvantage is theirpotentialfolliculartargeting. |
| Niosomes | Thesmallerparticle size of niosomes has theabilitytoincreasethecutaneousbioavailability of encapsulateddrugs. |
| Nanocrystals | Itsmostimportantadvantage is itshighdrug-stabilizerratios, resulting in approximately 100% drugloadingcapacity. |
| Nanogels | It has highbiocompatibility, highbiodegradability, enhancedpermeability, abilitytocrosstheblood-brainbarrier. |
| Micelles | Improvingdrugsolubilityincreasesthedistribution of bothhydrophilicandhydrophobicdrugs in the skin, anddrugaccumulation in hairfolliclesand skin. |
| Nanofibers | It has advantagessuch as highsurface-to-volumeratio, controlleddrugrelease, andincreaseddrugpenetrationintobiologicalbarriers. |

Due to the disadvantages of conventional formulations, exploration of potential applications of new carriers such as vesicles, lipidic particles and nano-sized carriers has become an integral part of the development of topical skin disease therapy8. Besides allowing an extended drug release, nano-sized carriers can provide greater efficacy by increasing drug stability until the desired site of action is reached. Nanocarrier properties affect the absorption capacity of the skin as each has an interaction mechanism based on its nature and physicochemical properties. For example, lipid nanoparticles are easy to form a film on the skin; this reduces the evaporation of water, increases skin hydration, increases the space between keratinocytes and consequently increases the permeability of lipid systems. On the other hand, polymer-based nanocarriers can easily pass through the hair follicle29. Solid-lipid nanoparticles, liposomes, niosomes, microemulsion, nanoemulsion etc. New topical systems such as nanocarriers are among the frequently used nanocarrier systems9.

Literature examples of innovative drug delivery systems used in infectious diseases of the skin are summarized in Table 2.

**Table 2:** Literature examples of innovative drug delivery systems used in infectious diseases of the skin.

|  |  |  |
| --- | --- | --- |
| **Drug Name** | **Carrier system** | **Results** |
| N'-((5-nitrofuran-2-yl)methylene)-2-benzhydrazide | Nanoparticle | Effective on tissueregenerationandbiofilm formation30 |
| Clindamycin | Nanoparticle | Increasedbactericidalactivityandacceleration of wound healing31 |
| Ionicliquidscontainingimidazoliumcations | Nanoparticle | High antibacterial activity32 |
| Antimicrobialpeptide LL-37 | Cubosome | High antibacterial activity33 |
| Gentamicin | Liquid Crystal | Antibiofilmactivitysustainedfor 2 days34 |
| Acanthospermumaustrale | AgNanoparticle | Higherantimicrobialactivityandlower cytotoxicity35 |
| Naftifine | Microemulsion | Significantincrease in pigskin permeability36 |
| Itraconazole | Microemulsion | Higherpermeabilitythan skin37 |
| Histidine coatedsilvernanoparticle | Microemulsion | Higherantibacterial activity38 |
| Voriconazole/ Sertaconazole | Microemulsion | Absorptionfromthedeeperlayers of the skin39 |
| Curcumin | Nanoemulsion | Decreases in *C. albicans* growth40 |
| Amphotericin B | Nanoemulsion gel | Effectiveandsafelocalizedreleaseagainstfungal infection41 |
| Essentialoil of *Stenachaeniummegapotamicum* | Nanoemulsion | Significantlyreduced minimum inhibitoryconcentrationand minimum fungicide concentration42 |
| Chalcone | Nanoemulsion | Tendencytoaccumulate in epidermis and dermis43 |
| Acyclovir | Organogel | High gellingpropertywithgood stability44 |
| Amphotericin B | Liposome | Potent anddose-dependent in vivoactivityagainstcutaneousleishmaniasisduetohighdrug accumulation45 |
| Azithromycin | Liposome | Success in thetreatment of cutaneousleishmaniasisduetoitsprolongedrelease ability46 |
| Tolnaftate | Liposomalgel | Higherpermeabilityandcure rate47 |
| Curcumin | Liposome | Moreeffective anti-inflammatoryandantibacterial activities48 |
| Fluconazole | Nanofiber | Fungi aresusceptibletodrug-laden samples49 |
| Nisin | Nanofiber | Abilitytoinhibitthegrowth of *S. aureus*strainsover a longperiod of time50 |
| Amphotericin B | Nanofiber | Significantantifungalactivityagainsteightfungal species51 |
| Vancomycin | Nanofiber | High drugretentionefficiencyandsuperiorantibacterial activity52 |
| Acyclovir | Nanofiber | HSV lesions had nosignificanteffect on healingorcrusting time28 |
| Chlorhexidine | Micelle | Effectiveantibacterialactivityagainst MRSA53 |
| Quaternaryammonium salt | Micelle | Complete recoverywithgoodantibacterialactivityandfewerinflammatory cells54 |
| Ketoconazole | Micelle | Increasedantifungalactivitywithincreasedaccumulation in the skin andincreaseddrug concentration55 |
| Clotrimazole, EconazoleNitrate, AndFluconazole | Micelle | Increased skin accumulationforeconazole nitrate56 |
| Fluconazole | Niosome | Longlastinglocalizedandsustained effect9 |
| Eberconazolenitrate | Microsponge | Higherantifungalpotentialcomparedtocommercial creams57 |
| NitroimidazoleCompound | Polymeric film-formingsystem | High concentration in the skin but ineffective in thetreatment of cutaneous leishmaniasis58 |

**Nanoparticles**

Nanoparticulate drug delivery systems can be used in the treatment of various diseases through their unique physicochemical properties and their ability to deliver therapeutic agents to desired areas in the body at a predetermined speed and time. There are various nanoparticulate release systems that have been studied as potential drug carriers for the treatment of many diseases. Some of these release systems are polymeric nanoparticles, metal nanoparticles, solid lipid nanoparticles, nanogels, micelles, nanocrystals, liposomes, nanocomplexes, dendrimers, nanocapsules, nanofibers, nanotubes and scaffold matrices59. A good nanoparticulate drug delivery system should include: Maximum drug bioavailability, tissue targeting, controlled release kinetics, minimal immune response, adequate drug loading capacity, good patient compliance60. The use of the ideal nano drug delivery system is decided according to the biophysical and biochemical properties of the drugs selected for treatment. However, attention should be paid to the toxicity exhibited by nanoparticles. Recently, nanoparticles have been used mostly in combination with natural products to reduce toxicity. Using green nanoparticles for drug release can reduce the side effects of drugs. In addition, changes in the size, shape, hydrophobicity and surface changes of nanostructures can further increase the bioactivity of these nanomaterials61.

There are two ways to deliver nanostructures as drugs: passive and self-delivery, in the first method, drugs are incorporated into the interior space of the structure through the hydrophobic effect. When nanostructural materials are targeted at a particular site, the intended amount of drug is released due to the low content of drug encapsulated in a hydrophobic environment. In the second, drugs intended to be released are conjugated directly to the carrier nanostructure material. This means that the timing of release is very important as the drug cannot reach the target site and may leave the carrier too quickly. Drug release mechanisms of nanocarriers; diffusion, solvent, chemical reaction and stimulus are in the form of controlled release61. Nanoparticles have many advantages such as more drug accumulation at the target site, increased physicochemical stability and controlled drug release5. Stable interactions with ligands, ability to change size and shape, high drug carrying capacity, and ease of binding of hydrophilic and hydrophobic substances make nanoparticles a suitable drug delivery system62. There are some disadvantages according to the types of nanoparticles. SLNs have disadvantages such as limited drug encapsulation, low physical stability, and initial drug release. Polymeric nanoparticles, on the other hand, have disadvantages such as the risk of toxicity due to the slow rate of polymer degradation and the necessity of purification for natural polymeric nanoparticles5.

**Solid Lipid Nanoparticles**

They are nano-lipid carriers in which the active therapeutic agent is dispersed in a lipid core matrix. Solid lipid nanoparticles can be prepared using high homogenization or by microemulsion. Solid Lipid Nanoparticles (SLN) are S/Y type emulsions containing solid lipids as oil phase. The smaller size of the lipid particles allows close contact with the SC, facilitating drug penetration into the skin and controlled release of the drug. Its formulations form a film on the skin and prevent water evaporation. As a result, the skin remains moist, and its barrier function remains intact. The lipid nanoparticles are spherical, so they have excellent lubricating behavior, preventing skin irritation and allergy. They have high drug retention capacity, and their release kinetics are well modulated. The active ingredients are protected against degradation by encapsulation. However, SLNs have a few limitations, such as having an unsuitable lipid structure in which a limited number of drugs are soluble9.

**Liquid Crystal Nanoparticles**

Liquid crystal nanoparticles (LCNPs) or lyotropic liquid crystals (LLCs) are self-assembled mesophases that exhibit properties of both ordered solids and isotropic liquids. They are also called mesophase, showing that it has a unique structure between the ordered solid phase and the true liquid phase. Liquid crystals are divided into three types: metallotropic, thermotropic and lyotropic. Lyotropic and thermotropic liquid crystals consist mainly of organic molecules. When the temperature is changed, the phase transition takes place in the thermotropic, whereas in lyotropic liquid crystals, temperature and concentration are responsible for the phase transition. LLCs are widely applicable for the delivery of a variety of therapeutics. LLCs can dissolve both water- and oil-soluble compounds. The liquid crystal-based formulation exhibits high hydration and easy dispersion compared to emulsion due to the similarity in LC and stratum corneum structures. The cubic phase system exhibits strong bioadhesive properties and forms a biological membrane-like structure on the skin when applied topically. The cubic phase is expected to interact with the SC forming a cubosomal lipid SC lipid mixture and form the cubosome depot that releases the drug in a controlled manner. The amphiphilic nature of the lipid and the presence of surfactant in the liquid crystals favor the interaction with SC and increase drug permeability. Drugs encapsulated in LCNPs interact with skin tissue and produce controlled release of the drug localized in the SC. The presence of water in the liquid crystals acts as a reservoir and provides hydration to the tissue63.

**Polymer Based Nanoparticles**

Polymeric systems are popular as they are more biocompatible and biodegradable. Various polymers and natural protein polymers such as poly lactic acid (PLA), poly glycolic acid (PGA), poly lactide co-glycolide (PLGA), poly caprolactone (PCL), and poly cyanoacrylate (PCA) are used for the preparation of polymeric drug delivery systems. PLA, PGA, PLGA, PCL and PCA polymers are FDA approved for human use due to their high biocompatibility. For application against CL, Amphotericin B (AmB) nanoencapsulation in PLGA/dimercaptosuccinic acid (DMSA) nanoparticles was developed and tested against C57BL/6 mice infected with L. amazonensis. Mannose-linked and AmB-encapsulated PLGA nanoparticles showed specific targeting on macrophage receptors, thus increasing the efficacy of the drug64.

**Metal Nanoparticles**

It is a cluster of small metal atoms with a size range of 10-100 nm. Advantages of metallic nanoparticles include strong plasma absorption, biological system imaging, detecting chemical information on metallic nanoscale substrate, surface enhanced Raman scattering. Disadvantages of metallic nanoparticles include impurity, difficulty in synthesis, particle instability, biological damage. Metallic nanoparticles can be easily regenerated using a minimum number of reagents that can control particle size, and can be prepared by a suitable method that is available and economical. Metallic nanoparticles of gold, nickel, silver, and iron in different shapes and sizes between 10-100 nm are drug carrier systems9.In a recent study by Andrade et al.30, chitosan nanoparticles loaded with a new active compound called N'-((5-nitrofuran-2-yl)methylene)-2-benzhydrazide were developed against multidrug resistant diseases. The optimized charged nanoparticles were found to be spherical and regular, with an average diameter of 321 nm, a polydispersity index of 0.18, a zeta potential of +37 mV, and a retention efficiency of 44%. The nanoparticles exhibited the best results for the inhibition of Staphylococcus aureus when compared with free drug and empty chitosan nanoparticles. In addition, nanoparticles were found to be effective on tissue regeneration and biofilm formation. As a result of the study, it was thought that this system, which was designed, could be used in the treatment of multi-drug resistant infections, especially in burnt skin areas.

Hasan et al.31 investigated the potential of polymeric nanoparticles (PNP) as a promising therapeutic alternative for skin infections. Mixed PNPs based on PLGA/PEI with loaded clindamycin, a semi-synthetic antibiotic derived from lincomycin, effective against aerobic gram-positive cocci and anaerobic gram-negative bacilli were developed. The developed nanocarrier was tested in an MRSA culture and ICR mouse model of cutaneous wound infection. They found that the developed PNPs could bind efficiently to the MRSA surface and increase the bactericidal activity of clindamycin. Moreover, clindamycin loaded PNPs were found to significantly accelerate wound healing and re-epithelialization in vivo study.

Takahashi et al.32 evaluated the potential of PNPs as a new carrier system against S. epidermis biofilm skin infections. Imidazolium cations are loaded into PLGA as the active compound. The researchers demonstrated that the developed PNPs have high antibacterial activity against biofilm-forming bacterial cells, and polymeric nanocarriers constitute a suitable drug delivery system to treat biofilm infections.

In the study of Boge et al.33, the use of cubosomes for topical delivery of antimicrobial peptide (AMP) LL-37 was investigated. Topical administration of AMPs is of great interest in the treatment of skin infections caused by bacteria such as Staphylococcus aureus. In addition to the proteolytic protection of LL-37, its bactericidal effect after enzyme exposure was investigated. Compared to pure LL-37, which exhibited proteolysis, the antibacterial property was retained despite exposure to the enzyme. Similarly, the inclusion of LL-37-loaded cubosomes in the ex-vivo wound infection model resulted in the highest antibacterial activity. Based on this study showing no skin irritation, LL-37 loaded cubosomes are approved for topical application.

In the study of Thorn et al.34, liquid crystals that respond to Pseudomonas infection were developed for the combination of glycoside hydrolase and antibiotics. The enzyme glycoside hydrolase (alginate lyase) and antibiotic (gentamicin) are loaded into infection-susceptible liquid crystals to treat Pseudomonas biofilms. Release of alginate lyase and gentamicin from glyceryl monooleate liquid crystals was triggered by the presence of Pseudomonas. The liquid crystal formulation showed sustained anti-biofilm activity for 2 days, equivalent to the free solution. The developed liquid crystals have been observed to be a promising release system for alginate lyase and gentamicin to combat topical Pseudomonas infections.

Mussin et al.35 prepared silver nanoparticles (AgNP) using the A. australe plant used in skin and soft tissue infections. The antimicrobial activity of AgNPs was tested against 298 fungi and bacteria that cause skin and soft tissue infections. AgNP solution showed higher antimicrobial activity and lower cytotoxicity compared to the synthesis components. It was observed that the antimicrobial activity of AgNPs was dependent on silver, not on the metabolites of the aqueous extract on the surface of the nanoparticles.

**Emulsions**

Emulsions are metastable colloidal systems consisting of droplets of one liquid dispersed in another immiscible liquid. In general, there are three main types of emulsion systems: Macroemulsions, nanoemulsions, and microemulsions65.

**Microemulsions**

They are stable, translucent, and isotropic oil dispersions in water stabilized by surfactants and co-surfactants for topical and transdermal application of drugs with a droplet size of 0.1-1.0 µm. The presence of oils and surfactants in the microemulsion formulation facilitates drug permeability throughout SC9.

Emulsion and microemulsion systems are different because, although they may exhibit kinetic stability, they are thermodynamically unstable and may form phase separation in the long run. In addition, the macro view of both systems is different. Emulsions are cloudy while microemulsions are transparent or translucent. Regarding the manufacturing process, emulsion systems require a large amount of energy. Therefore, commercial production costs are higher than for microemulsion systems66. Microemulsions form spontaneously when appropriate amounts of the ingredients are mixed. In most cases, no external mechanical energy source is needed. Microemulsions can be divided into S/Y type, Y/S type and two continuous types. In S/Y type microemulsions, water is the dispersed phase while oil is the continuous phase. In Y/S type microemulsions, oil is the dispersed phase while water is the continuous phase. In two continuous microemulsions, the aqueous and oily phases are intertwined. S/Y type microemulsions are usually prepared by mixing surfactants, co-surfactant, and oil, followed by light titration with distilled water. Microemulsions can be classified according to the type of oil phase used67.

Because microemulsions are liquid in nature, they are advantageous in terms of gastrointestinal stability. Small droplet size increases the surface area/volume ratio for drug absorption. In addition, these small droplet sizes can resist gravity separation and thus increase the stability of the microemulsion system. The small droplet sizes of microemulsions also allow for release by a wide variety of routes of administration. Another important advantage of microemulsion systems is their ability to dissolve poorly soluble drugs in water. It is possible to include hydrophilic and hydrophobic pharmaceutical active ingredients in microemulsions containing both a hydrophilic and hydrophobic phase. Y/S type microemulsions are well suited for lipophilic drug release, while S/Y type microemulsions are well suited for hydrophilic drug release. Microemulsions are also an economical drug delivery system. Its ability to form spontaneously provides a cost-effective production method. Surfactants and oil components are readily available and often economical65.

Microemulsion systems may not always be a suitable delivery method for substances that do not dissolve in hydrophilic or hydrophobic environments. Minerals are the best example of this. Pharmaceutical active ingredients such as iron and calcium are likely to cause suspension if added to a microemulsion system. Microemulsions also require the presence of emulsifiers at a slightly higher concentration than their nanoemulsion counterparts. Some emulsifiers show toxicity. Because microemulsions are sensitive to temperature and salinity changes, they may undergo phase changes when exposed to higher or lower temperatures or salinity concentrations than normal. This may lead to phase separation65.

In the study of Erdal et al.36 physicochemical characterization was carried out by preparing microemulsions containing oleic acid (oil phase), Kolliphor EL or Kolliphor RH40 (surfactant), Transkutol (common surfactant) and water. C. albicans ATCC 10231 and C. parapsilosis were used to evaluate the antifungal susceptibility of naftifine loaded microemulsions. The in vitro skin transfer of naftifine from microemulsions was investigated and compared with its traditional commercial formulation. It was observed that the microemulsion formulation containing Kolliphor RH40 as co-surfactant significantly increased the permeability of naftifine through pig skin compared to the commercial formulation.

Itraconazole is an antifungal agent used in the treatment of ringworm infection. It shows lower permeability when applied topically. Therefore, Patel et al.37 prepared a microemulsion to increase the permeability of itraconazole through the skin. The microemulsion was prepared using eucalyptus oil, tween 20 and methanol as oil phase, surfactant and co-surfactant, respectively. In vitro antifungal studies have been performed against Candida albicans. As a result, it was observed that itraconazole provided higher permeability to the skin when applied via microemulsion.

Chhibber et al.38 prepared a microemulsion-based topical application system containing histidine-coated silver nanoparticles to treat murine wound infection induced by K. pneumoniae, a bacterial species that spreads easily in the hospital environment and shows high resistance to antibiotics. A mixture of oleic acid, tween 80 (surfactant), co-surfactant (ethanol) and water was used to develop the microemulsion. The results showed that histidine loaded into the microemulsion provided greater antibacterial activity in vivo.

Qurt et al.39 designed a microemulsion formulation to increase the permeability of both voriconazole and sertaconazole to the skin due to its high solubility and permeability enhancing properties. oleic acid (oil), tween 80 (surfactant) and ethanol (co-surfactant) based microemulsion systems have been developed. Antifungal activity was evaluated against Candida species. It has been observed that the microemulsion formulation of both agents can be absorbed in the deeper layers of the skin. The results suggest that the microemulsion may be a potential colloidal carrier to enhance the topical release of voriconazole and sertaconazole.

**Nanoemulsions**

Nanoemulsions (NE) are Y/S, S/Y dispersions of two immiscible liquids stabilized using a suitable surfactant. The resulting mean droplet diameter is usually < 500 nm. The small droplet size gives it a clear or hazy appearance that differs from the milky white color associated with the coarse emulsion. NEs can be made into various dosage forms such as liquids, creams, sprays, gels, aerosols, foams. Their long-term physical stability is a direct result of the small droplet size, which disrupts instability states such as creaming, precipitation, and coalescence68.

During the preparation of NE, a suitable emulsifier or emulsifier combination is added to achieve long-term stability. Emulsifiers are surface-active molecules and allow easy dispersion, adsorbtion, and rearrangement at the interfacial regions by reducing the interfacial tension69. Emulsifier selection is made on the basis of their solubility in oil and aqueous phases, HLB value, and lower toxicity profile70. NE preparation processes fall into two main categories, high and low energy emulsification methods. Ultrasonic emulsification, microfluidization, and high-pressure homogenization are considered high-energy methods, while high-speed homogenization, phase inversion temperature, and phase inversion composition are classified as low-energy methods71.

Because NEs have submicron particle size, they can easily penetrate through skin pores and reach the systemic circulation. NEs have the advantages of low toxicity, non-irritationand long-term stability, as well as being applicable using different routes of administration, particularly in dermal and transdermal drug release. Penetration enhancers containing NE can increase skin penetration through different mechanisms, such as increased drug solubility in the carrier, SC specific carrier uptake, and fluidization, alteration, and dissolution of SC lipids. NEs with oils and surfactants in their formulations have the ability to highly enhance transdermal delivery of both hydrophilic and lipophilic drugs. In addition, it has advantages such as controlled and long-term drug release, ease of self-administration, and the absence of gastrointestinal side effects5.

There are disadvantages that should be considered before NEs are prepared. Foremost among these is the inability of NEs to dissolve substances with high melting points. In addition, the components to be used in the development of NE must be absolutely non-toxic. This appears to be a limiting problem. NEs prepared by low energy methods often require large amounts of surfactant to stabilize the droplets. In such cases, heavy use of surfactants can cause biomembrane fluidization, negating their internal use. The price-effectiveness of NE production is often expensive68.

Lewinska et al. 40 designed NE stabilized with N-oxide surfactants for topical application. Curcumin, derived from Curcuma longa L., has traditionally been used as an antimicrobial phytochemical. The antifungal activity of curcumin-loaded formulations against C. albicans was evaluated. Reductions in C. albicans growth were seen when cultures were treated with both uncharged and curcumin-loaded NE. A differential scanning calorimetry study was also conducted to find the interactions of NEs with SC. As a result, it has clearly shown that Y/S type NE systems produced without a co-surfactant are viable, thanks to a successful selection of N oxide surfactant.

Hussain et al.41 prepared a NE gel for topical application of AmB and evaluation of antifungal activity. A series of NEs were prepared using cefsol 218 oil, Tween 80 and Transcutol P by slow spontaneous titration. Antifungal activity against three fungal strains was investigated using the in vitro well agar diffusion method. Histopathological evaluation was performed to investigate toxicological potentials in rats. The in vitro drug release profile results effectively demonstrated the sustained release of AmB compared to the free drug solution. In vivo histopathological examination has shown that formulations for cutaneous infection are safe and effective compared to oral administration. Thus, the NE gel appeared to provide effective and safe localized release of AmB against fungal infection.

Danielli et al.42 analyzed the chemical composition of the essential oil of Stenachaeniummegapotamicum to evaluate the antifungal activity of pure oil and NE. NE was obtained by self-emulsification and exhibited a translucent appearance, pH 5.14, particle diameter of 210 nm, and polydispersity of 0.369. Significantly reduced minimum inhibitory concentration and minimum fungicide concentration were observed in NE containing the essential oil of S. megapotamicum. Compared with the pure oil activity, it was observed that the nanoparticulate system improved the oil activity.

Coelho et al.43 prepared chalcone-containing NE for the development of molecules with leishmanicidal activity. Trans chalcone nanoemulsion and 3'-(trifluoromethyl)-chalcone were prepared using a spontaneous emulsification method. All formulations contain medium chain triglycerides, soybean lecithin, glycerol, ethanol, poloxamer, and water in the aqueous phase as the oily core in the organic phase. It has been observed that NE containing chalcone tends to accumulate in the epidermis and dermis. The results show that NEs, especially 3'-(trifluoromethyl)-chalcone, are potential candidates for the development of new antileishmanial drugs.

Rajpoot et al.44 developed an acyclovir-loaded nanoemulsion-based organogel (NEOG) system for the effective treatment of HSV infection via topical application. The NEOG system of acyclovir was developed using an oil (isopropyl myristate), surfactants (Span 60/Tween 80) and doubly distilled water as the aqueous phase. Drug-loaded NEOG formulations were prepared using the aqueous titration method. The developed NEOG acyclovir system showed high gelling properties with good stability.

**Liposomes**

In 1965, Bangham A first discovered that phospholipid molecules can spontaneously form closed bilayer vesicles in water. Shortly thereafter, liposomes ranging in size from 5 to 200 nm were reported to encapsulate hydrophilic or lipophilic drugs in the aqueous phase or bilayer membrane phase using the affinity of different segments of the vesicles. Subsequently, liposomes were introduced as drug delivery systems. Liposomes are composed of classical lipid molecules or novel lipid molecules, both of which belong to amphiphilic molecules and usually consist of a hydrophilic head, hydrophobic tail, and bonds. The hydrophilic heads of lipid molecules can be divided into three types according to their charge: cationic, neutral and anionic72. Liposomes are potent drug delivery systems due to their biocompatibility, biodegradability, non-toxic and non-immunogenic nature as well as their structural versatility. The amphiphilic character of phospholipids in solution mimics natural cell membranes, allowing excellent interactions between liposomes and mammalian cell membranes. Additional advantages of liposomes include high drug transport capacities, self-assembly, and a wide range of physicochemical and biophysical properties that can be modified to control their biological properties. The drug loaded into the liposome is protected against physiologically occurring events such as enzymatic degradation, chemical and immunological inactivation, and rapid plasma clearance. Because the drug is in the liposome, exposure of undesirable side effects to healthy tissue is minimized compared to the free drug form73.

Stability is considered a challenging process for liposome preparation, storage and subsequent administration steps. Potential instability issues of liposomes typically relate to oxidation and/or hydrolysis of lipids, drug leakage, aggregate formation, and liposomal fusion. The major limitation of liposome application is the lack of identification of a suitable method for large-scale production, known as scale-up. Another limitation of liposomes is their sterilization, which is a challenging process due to their susceptibility to physical and chemical degradation. Methods for liposome sterilization must achieve a compromise between inactivation of microorganism contamination and degradation of the liposomal product. Sterilization methods should not affect the physical and chemical properties of the liposomal formulation and should be destructive for microorganisms73.

AmBisome (LAmB), a liposomal formulation of AmB, is a second-line therapy for the parasitic skin disease CL. In this study, the skin pharmacokinetics of LAmB were compared with the deoxycholate form of AmB (DamB) in murine models of Leishmania major. A single dose of 1 mg/kg LAmB or DAmB was administered intravenously to uninfected and L. major infected mice. Plasma concentrations and exposure were much higher for LAmB than for DAmB and did not reflect changes in skin tissue levels for either formulation. Drug concentrations at the target site were similar after a single intravenous dosing of the individual AmB formulationsbut were 3 times higher for LAmB than for DAmB after 5 administrations of the same dose. In conclusion, intravenous LAmB was found to have potent and dose-dependent in vivo activity against CL due to relatively high drug accumulation within the lesion45.

Naeini et al.46 aimed to evaluate the efficacy of a combination of liposomal and oral azithromycin against CL as the first clinical trial. Liposomes were prepared by a hydration dehydration method. This evaluator-blind, randomized clinical trial was conducted in outpatients at the Leishmaniasis Skin Diseases and Leishmaniasis Clinic. In the oral+liposomal group, liposomal azithromycin was applied twice a day as 0.2-0.5 mL (6 to 15 mg) to form a thin drug layer on the lesion surface, depending on the lesion size. All participants received 250 mg of azithromycin or 8 mg per kg twice daily for 4 weeks. The duration of treatment was 4 weeks for each group, and the patients were followed up once a week during the treatment, then 2 and 6 times thereafter. Until the end of the treatment period, no patient showed any signs of allergy or skin inflammation, and there were no complaints of inflammation or skin problems afterwards. In conclusion, the combination of topical liposomal and oral azithromycin has shown success in the treatment of CL due to its biodegradability, biocompatibility, non-toxic, non-immunogenic nature and prolonged release capability of liposome-loaded azithromycin.

Meghana et al.47 developed a liposomal gel containing the antifungal tolnaftate for the treatment of topical fungal infections. Preparation of liposomes with soy lecithin containing tolnaftate was accomplished by dried thin film hydration. Prepared liposomes were added to carbopol gel under stirring to obtain 1% tolnaftate liposomal gel. Formulated liposomal gels have shown effective absorption and cure rates in the topical fungal infection treatment compared to marketed ones. It has been observed that the higher permeability and cure rate is due to the smaller particle size.

Ternullo et al.48 developed an effective liposomal formulation intended for transdermal delivery of curcumin for the treatment of inflamed and infected wounds. Neutral, cationic and anionic deformable liposomes containing curcumin were prepared and the role of liposomal surface charge was evaluated in ex vivo skin penetration studies using full thickness human skin. In vitro anti-inflammatory and antibacterial activities of curcumin-loaded liposomes were evaluated. To investigate the effect of liposomal surface charge on skin penetration of curcumin, deformable liposomes with neutral surfaces were used as controls. All prepared deformable liposomes showed relatively high curcumin uptake and, in ex vivo skin penetration studies, provided optimal curcumin concentration at the skin site while limiting systemic absorption. Cationic deformable liposomes exhibited the longest curcumin penetration through full-thickness human skin, resulting in high absorption of curcumin in the skin. In conclusion, all liposomal formulations exhibited concentration-dependent anti-inflammatory and antibacterial activities that were more potent than non-liposomal curcumin activities.

**Nanofibers**

Nanofibers are one of the groups of nanomaterials that have two similar outer dimensions at the nanoscale (≤100 nm) and a third dimension that is significantly larger. Nanofibers exhibit many great properties such as large surface area, surface functionalization possibility, adjustable porosity, wide choice of materials and superior mechanical performance. Nanofibers provide great flexibility in choosing biodegradable or non-biodegradable materials to provide properties such as better control over drug release kinetics for drug release applications. There are possibilities of loading enzymes, antimicrobial peptides, antibiotics and growth hormones into nanofibers or the core of nanofibers. Nanofiber scaffolds provide cells with many favorable properties such as high porosity, large surface area, biocompatibility, mechanical properties, which are necessary for tissue regeneration and sustained release of drugs or growth factors. The loading of bioactive compounds into nanofibers provides a great environment for treating infections at wound sites, inhibiting bacterial biofilm formation, prolonging drug release and shortening the wound healing process. Nanofibers provide three-dimensional architecture with desirable surface properties, as well as mechanical strength and physiological acceptability74,75,76.Semnani et al.49 investigated the possibility of using fluconazole locally and as a carrier with the help of polymeric nano and micro fibers in the treatment of infections caused by Candida albicans. For the electrospinning of the PVA nanofibers, 70:30 water/ethanol was used as the solvent. After the solutions were prepared, they were placed in a 1 ml insulin syringe with a tip diameter of 22 gauge, and then the syringe was placed in the electrospinning apparatus. Electrospinning was carried out at a voltage varying between 12 KV and a collector distance of 15 cm. The morphology of the electrospun fibers and the diameter of the fibers were examined by scanning electron microscopy (SEM). Electrospinning of 8% and 10% PVA solutions resulted in uniform and bead-free nanofibers and microfibers. In the release test, it was observed that the release was carried out rapidly at the beginning of the release due to the high specific surface area of ​​the fibers and the presence of drug on the fiber surface. As time passed, the rate of release decreased and ended after about 7 hours. Finally, in vitro testing revealed that the fungus was sensitive to drug-loaded samples.

Asgari et al.51 produced AmB-loaded core-shell nanofibers using PVA, chitosan, AmB as cores and PEO and gelatin as shell-forming components to minimize AmB side effects. After the solutions were prepared, they were transferred to syringes and placed in pumps. The distance to the collector was set as 14 cm and a voltage of 22 kV was applied between them. Nanofibers with different drug concentrations were prepared and their morphologies were evaluated by SEM. It was observed that nanofibers with 3% and 6% drug concentrations had a bead-free and homogeneous appearance. By increasing the drug concentration to 9%, weak fibers with large diameter and low density were formed. According to the agar anti-diagram assay, the nanofibers showed significant antifungal activity against eight fungal species, inducing zones of inhibition of 1.4-2.6 cm, comparable to AmB standard discs. The drug-loaded nanofibers also showed remarkable activity against parasites. The results obtained show that AmB-loaded core-shell nanofibers are a suitable drug delivery system for use in the treatment of superficial fungal infections and CL.

Fathi et al.52 prepared vancomycin loaded nanofibers to reduce the toxicity of vancomycin used in the treatment of MRSA skin infections. The nanofibers were prepared by electrospinning. Certain amounts of sodium alginate and PEO were separately dissolved in distilled water under magnetic stirring for 48 hours to ensure complete dissolution. In order to obtain a PEO/sodium alginate mixture, a homogeneous solution was obtained by mixing the PEO and sodium alginate solutions at a ratio of 1:1 for 2 hours. The pump flow rate was set at 1 mL/hr. The distance between the needle tip and the collector plate was set as 15-20 cm. The voltage ranged from 15 to 23 kV until a stable Taylor cone was obtained. The surface morphology of the electrospun nanofibers was visualized by SEM. The in vivo antibacterial activity of vancomycin-loaded nanofibers was evaluated compared to free drug solution in rats using a superficial skin infection model of MRSA. As a result of the study, the optimized vancomycin loaded nanofibers exhibited high drug retention efficiency. Compared to the free vancomycin drug solution, the vancomycin loaded nanofibers were observed to have superior antibacterial activity against MRSA.

Nucleoside analogues such as acyclovir are common drugs prescribed for the treatment of herpes lesions. Given the poor water solubility and low transdermal permeability of acyclovir cream, the potential of nanofiber patches to improve bioaccessibility has been explored. In a study conducted at Isfahan University of Medical Sciences28, two drug formulations (acyclovir nanofiber patch and acyclovir cream) were compared in the treatment of recurrent diseases. As a result of the study, it was observed that acyclovir nanofiber patch and routine acyclovir formulation did not have a significant effect on the healing or crusting time of HSV lesions. However, the limited number of participants and the inability to compare acyclovir patch with acyclovir cream in terms of release profile, penetration percentage and in vitro absorption capacity may have caused this result.

**Micelles**

Polymeric micelles are nano-sized drug release systems characterized by a core-shell structure resulting from the self-assembly of amphiphilic block copolymers in aqueous solution. In the diluted aqueous solution, the amphiphilic molecules exist separately, and the amphiphiles work as surfactants, reducing the surface tension at the air-water interface. The critical micelle concentration (CMC) is defined as the minimum polymer concentration in solution leading to micelle formation. Accordingly, while micelles are stable at higher polymeric chain concentration than CMC, disassembly of the system is observed after dilution below CMC. The CMC value is the most important parameter that defines the thermodynamic stability of the micelle. The most commonly used polymers for micelle growth are amphiphilic diblock copolymers (polystyrene and poly(ethylene glycol)) and triblock copolymers (poloxamers). The hydrophilic portion usually consists of PEG, but other polymers such as poly(vinyl pyrrolidone), poly(acryloylmorpholine) or poly(trimethylene carbonate) are also used. The hydrophobic segment can be made from polyesters such as poly(propylene oxide) or poly(ɛ-caprolactone) or polymers and copolymers of glycolic and lactic acids77.

Drugs may be encapsulated with micelles during their formation or in a second step, depending on the method used for their preparation and the physicochemical properties of the drug. The easiest preparation method is direct melting. Other methods are solution casting followed by emulsion and film hydration by dialysis, solvent or co-solvent evaporation. Method selection depends on both polymer and drug properties. Hydrophobic active substances dissolve in the micelle lipophilic core, while moderately polar or highly hydrophilic molecules occupy an intermediate position or at the surface of the system, respectively. Often, hydrophobic drugs are loaded into the inner core. In hydrophobic drugs, the amount loaded depends on the hydrophobic interactions that occur between the drug and the micelle core. In specific cases, the drug can also be covalently attached to the polymer (polymer-drug conjugate)77.

Small size, easy preparation and good dissolution properties make polymeric micelles used carriers for different routes of administration. They can improve drug bioavailability and produce a controlled and targeted drug release that is beneficial for reducing side effects. The surfaces of micelles with high drug loading capacity can also be functionalized with specific molecules for active targeting77.

Thermodynamically self-forming micelles are formed with reversible limits and can be broken down by various destabilizing factors. Depending on the route of application, the micelles face different problems. For example, in the case of intravenous administration, high dilution, presence of serum can be observed with the stress of injection. In mucosal and skin conduction, interaction with mucus and sebum can be observed. At the same time, the preparation methods of micelles are complex and costly77.

Bachhav et al.56 investigated the antifungal activity of new aqueous micelle dispersions of different antifungal drugs clotrimazole, econazole nitrate and fluconazole. Micelles were developed using new amphiphilic block copolymers (methoxy poly(ethylene glycol)-hexyl substituted polylactide). These nanometer-sized micelles showed a tendency to accumulate in the skin for econazole nitrate.

Albayaty et al.53 investigated the delivery of chlorhexidine to S. aureus, MRSA and S. epidermidis biofilms with both single and mixed micelle systems based on polyvinyl caprolactam (PCL)-PEG copolymers. Chlorhexidine along with the polymers was dissolved in 1 mL of acetone, then the organic solution was dispersed into the aqueous phase. The emulsion was stirred at 100 rpm for 24 hours at room temperature to remove the organic solvent from the mixture by evaporation. The resulting micelle systems were centrifuged at 4499 x g for 15 minutes and filtered using a 0.45 µm filter membrane to remove all aggregates. Validation of the antibiofilm activity of chlorhexidine micelle systems was performed on a 3D artificial dermis model. Micelles loaded with chlorhexidine were found to be more effective against MRSA.

He et al.54 developed a charge-convertible quaternary ammonium salt-based micelle system for in vivo bacterial disinfection. It is formed by combining two amphiphiles with opposite charges and shell crosslinking strategy. It was thought that the surface charge of the quaternary ammonium salt-based micelle would be positively changed in response to the acidic environment at the sites of infection, and then could target negatively charged bacteria. In vivo antibacterial administration of quaternary ammonium salt-based micelle was studied in BALB/c mice with a subcutaneous abscess model infected with S. aureus. For the micellar-treated group, the damaged skin was almost completely healed in the same time period. To confirm antibacterial activity, pus was collected from the abscess site of mice on days 2 and 5. In the group that received mycelial treatment, it was observed that the bacteria died almost completely after 5 days. At the same time, it was observed that the dermal tissues in the abscess areas were completely healed with fewer inflammatory cells in the group treated with mycelium. As a result, micelles formed with quaternary ammonium salts showed good antibacterial activity.

Deng et al.55 prepared ketoconazole with loaded Y-shaped monomethoxy poly(ethylene glycol)-block-poly(ɛ-caprolactone) micelles by thin-film hydration method to improve its water solubility. Hydrophobic ketoconazole could be embedded in a hydrophobic core through its hydrophobic interaction with the poly(ε-caprolactone) chain, while hydration of the hydrophilic polyethylene glycol shell resulted in increased water solubility of ketoconazole. In vitro antifungal studies were performed against Candida albicans on Sabouraud's agar medium by the plate method. The percentage of inhibition increased with increasing drug concentration. Ex vivo skin permeation and retention studies were performed on mouse skin by the Franz diffusion cells test to evaluate the effect of micelle absorption and deposition in the skin. Micelles loaded with ketoconazole were found to show increased accumulation in the skin. At the same time, the micelle promoted cutaneous absorption of ketoconazole with a lower blood distribution compared to ketoconazole cream. In addition, no skin irritation was observed in vivo during treatment with mycelium. In conclusion, micelles can be a good drug release system for ketoconazole.

**Niosomes**

It is a kind of spherical lipid vesicles prepared by nonionic surfactants. By interacting with SC, they cause a decrease in transepidermal water loss. Its absorption into the skin depends on the type of surfactant, the properties of the drug used, and the morphological characteristics of the niosomal formulations. The degree of permeability through the skin depends on the interaction between the niosome and the skin, the nature of the drug, the composition and morphology of the noisome. Thanks to their stable bilayer structure, niosomes increase product stability by protecting the encapsulated therapeutic agent from proteolytic enzymes, surrounding pH and osmotic agents. Due to their unique amphiphilic properties, they can trap a wide variety of drugs. Besides their advantages, niosomes exhibit some disadvantages such as aqueous niosomal suspensions can fuse, leaking encapsulated drugs, and hydrolysis of the drug leading to limited stability78,79.

Niosomes have proven to be an effective system for antifungal drugs. Fluconazole loaded niosomes prepared using different surfactants (Span 40, Span 60 and Brij 72) revealed long-term localized and sustained effects of fluconazole9.

**Microsponge Gel**

It is a unique drug delivery system consisting of microporous pellets with a size range of 10-25 μm, providing control of the release of encapsulated drugs. These are small particles composed of natural or synthetic polymers with a high drug loading capacity equal to their own weight. They are considered biocompatible, non-irritating, non-allergenic, and safe for the skin, making them suitable for topical drug release. Because microsponges are small porous microparticles capable of trapping a wide variety of active ingredients, the interconnected pores provide prolonged release of the encapsulated drug over time. However, residues of residual monomers during microsponge synthesis can be toxic and harmful to health9.

Fluconazole has excellent antifungal activity but is not clinically preferred due to skin irritation following topical application. Fluconazole loaded microsponge formulation was developed by liquid-liquid suspension polymerization using different polymers (styrene and methyl methacrylate). Microsponge has proven to be an excellent formulation for the controlled release of fluconazole9.

Shamshina et al.57 found in their study that ebercanazol nitrate-loaded microsponge in ethyl cellulose gel showed controlled drug release, no signs of skin irritation, and higher antifungal potential compared to commercial creams.

**Film Forming Systems**

As an alternative approach to drug delivery systems, polymeric film forming systems (FFSs) have been developed that are applied directly to the skin and form a thin, cosmetically acceptable, and transparent film as the solvent evaporates. Film-forming formulations can lead to sustained drug release via two mechanisms. In the first, the drug retains some solubility in the remaining film, which facilitates prolonged contact with the skin from the reservoir on the skin. Second, modification of the formulation after application to the skin enhances rapid drug transfer to the SC, which then creates an intradermal reservoir. From here, the drug gradually spreads into the skin layers. Both strategies facilitate drug release into the local skin site over a long period of time, allowing for less frequent applications and increasing patient compliance. The advantage of an FFS is that as the solvent evaporates after application to the skin, the concentration of drug in the remaining vehicle increases, potentially creating a temporary state of supersaturation in either the skin or the SC. Along with improved skin-film contact, an FFS can improve dermal distribution of the drug58.

Bocxlaer et al.58 investigated film-forming systems for the delivery of DNDI-0690, a nitroimidazole compound with potent activity against Leishmania causing CL. The efficacy of FFSs was evaluated in vivo in the L. major BALB/c mouse experimental model of CL. Given the potent in vitro activity of DNDI-0690, the findings suggest that insufficient amounts of the drug reach parasites in the dermal layers of the skin upon topical application. Overall, although these FFS formulations resulted in higher DNDI-0690 concentrations in the skin compared to the conventional formulation, the concentrations were insufficient to repel Leishmania parasites from the skin and resolve CL.

**Polymeric Microneedle Systems**

Polymeric microneedle mediated sustained release systems (MN@SRS) is a system that combines the advantages of polymeric MNs and the sustained release technique. MN@SRS is minimally invasive, significantly preventing needle stick injuries and pain caused by subcutaneous injections. It is also designed as self-administration, meaning there is no requirement for qualified medical personnel. More importantly, MN@SRS with different release properties can be produced by polymers with different degradation patterns. Four typical MN@SRS categories have been developed. One is called long-acting encapsulated or coated MNs. These MNs are only used as tools to pierce the skin and then implant the preloaded cargoes. The sustained release property is achieved by packaged or coated drugs. Another is polymeric-based sustained release MNs fabricated with a long-acting polymer that takes the form of sustained release via the host MN polymer. Dual continuous release MNs is the third strategy of MN@SRS. These MNs load long-acting packaged drugs into sustained release MNs to achieve a longer sustained release period. Tier-based warehouse MNs are the fourth strategy to achieve sustained release of MNs. In this design, the drug is loaded onto the backsheet as a reservoir instead of the needles. MN@SRS is promising for the treatment of fungal infection of the skin80.

**Nanogel**

Nanogel is defined as nanoparticles composed of cross-linked hydrophilic structures. Their size varies between 20-200 nm. Oral, topical, vaginal, ocular etc. they can be applied in different ways. They show better skin permeability due to their smaller size and soft material, and diffusion-based swelling allows for the desired drug release behavior. In general, they have excellent biocompatibility and high hydrophilic drug load. Some nanogels have a hydrophilic nature, which limits the good encapsulation ability of hydrophobic drugs. The nanogel has been found to be suitable for administering a wide variety of drugs, including hydrophilic and lipophilic drugs. The most common limitations of nanogel are that although nanogel processing is not very expensive, it is difficult to separate surfactant and solvent from the finished product9.

**CONCLUSION**

Infectious diseases of the skin are a group of diseases that are difficult to treat and highly contagious. Innovative drug delivery systems have been developed due to the inadequacy of formulations such as creams, ointments and gels used in the treatment of these diseases. These systems are generally nano-sized structures and exhibit superior efficacy in the treatment by being better absorbed into the skin. Nanoparticles, liposomes, microemulsions, nanoemulsions, liposomes, micelles, nanofibers can be given as examples of these systems. Various nanoparticles have been designed for use in resistant skin infections. As a result of these studies, it was observed that antibacterial activity increased and tissue regeneration accelerated in wounds and burns. At the same time, nanoparticles do not cause any irritation to the skin. However, due to the toxicity risk of nanoparticles, cytotoxicity tests should be emphasized in studies to be carried out. Microemulsion systems have been developed by using various antifungal agents to increase the percutaneous percutaneous use of antifungal drugs. Studies have shown that the permeability of drugs through the skin has increased significantly compared to conventional formulations. At the same time, it was observed that the antibacterial activity of microemulsions increased in studies against bacterial infections of the skin. However, in the studies to be carried out while designing microemulsions, attention should be paid to the risk of toxicity that may be caused by the emulsifier concentration. In studies with nanoemulsions, nanoemulsion gels have been developed against bacterial, fungal and viral skin infections. As a result of the studies, high activity was observed. More studies can be done with nanoemulsions for use in infectious diseases of the skin. Liposomes are one of the most popular drug delivery systems recently. LAmB is an FDA-approved liposomal formulation for CL, a parasitic skin disease. This formulation provides an effective treatment by increasing drug accumulation in the skin. In other studies with liposomes, liposomes have shown superior properties in the treatment of infectious diseases of the skin due to their biocompatibility, non-toxic and non-immunogenic nature. In studies with nanofibers, increased antibacterial and antifungal activity has been observed due to the large surface area and long-term drug release of nanofibers. In studies with micelles, the treatments were successful and it was seen that the skin developed less inflammatory response in the infection. More studies can be done for infectious diseases of the skin using micelles. As a result, innovative drug delivery systems designed for use in infectious diseases of the skin have shown success in treatment by exhibiting far superior properties compared to conventional formulations. However, while designing the formulation, care should be taken that the substances to be used do not show cytotoxicity. At the same time, since these systems are complicated and costly, new techniques are needed for industrial-scale production.

**CONFLICT OF INTEREST**

No conflict of interestassociatedwiththiswork.

**AUTHOR'S CONTRIBUTION**

Concept – İ.E.G., B.A.K.; Design – İ.E.G., B.A.K.; Supervision – İ.E.G.; Resources – A.T.; LiteratureSearch – A.T.; Writing – A.T., İ.E.G., B.A.K.; Critical Reviews – İ.E.G., B.A.K

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