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REVIEW ARTICLE

INNOVATIVE DRUG DELIVERY SYSTEMS FOR INFECTIOUS DISEASES OF THE SKIN

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Abstract

Introduction: Skin is the organ of the body that is exposed mostly to the microorganisms. Bacteria, fungi, and viruses are usually responsible for the infection of the skin. Due to lack of penetration through the *stratum corneum* of conventional systems used in infectious diseases of the skin leads to a decrease in bioavailability. For this reason, nanoscale drug delivery systems that could be used in infectious diseases of the skin are currently being investigated.
Areas covered: In this review, innovative studies conducted over the years are presented. New topical formulations such as nanoparticles, microemulsions, liposomes, nanofibers and micelles etc are widely used and topic of research for many researchers.
Conclusions: Studies have shown that the smaller size and control of these delivery systems provide more effective treatment by increasing drug penetration into the skin. It has been found that drug delivery systems provide a better antimicrobial effect, especially in resistant infections caused by MRSA.
Keywords: drug delivery systems, modified release dosage forms, skin infectious diseases, topical.

INTRODUCTION

In line with the different cell types it has, the skin basically forms a three-layered structure: epidermis, dermis and hypodermis[1]. The *stratum corneum* (SC), is a lipid structured layer containing multiple corneocyte layers in the epidermis[2] and drug is absorbed through it. Basically it acts as the barrier in transdermal delivery of drugs[3]. Conventional formulations like gels and creams show poor penetration while passing through the SC. For this reason, it is necessary to develop innovative drug delivery systems[4]. Innovative drug delivery systems, being nano-sized, penetrate the skin better and increase absorption. Due to localized drug accumulation residence time of drugs gets increased in the skin. It reduces the side effects of the drug by limiting the systemic absorption. It also allows for controlled drug release[5]. The skin is an organ open to microorganisms, and bacteria, fungi and viruses are among the pathogens that cause skin infections[6,7]. 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 micelles[8,9].

In this review, studies with innovative drug delivery systems for infectious diseases of the skin are presented with an overview.

INFECTIOUS DISEASES

Bacterial Diseases of the Skin

Streptococcus species are responsible for many skin and soft tissue infections. 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[10,11]*Staphylococcus aureus* is responsible for it[12]. Ecthyma gangrenosum refers to the sepsis state of *P. aeruginosa*. Localized lesion gets developed rapidly, initially vesiculobullous that transforms within 12-24 hours to ulceronecrotic lesion[13]. However, lesions remains in less number but may multiply in different stages. Acute bacterial folliculitis associated with one or more hair follicles infection. *S. aureus* is responsible for it. It is the most common form of superficial folliculitis. It is 'Impetigo of Bockhart' and is caused by *S. aureus*. Deeper folliculitis in depth may leads to chronic condition[11].
An abscess is the condition of pus in the body tissue[11]. In mostly cases *S. aureus* is responsible for it[14]. In case

of accessibility to the affected body part, it can be treated by the means of drainage[11].

Cellulite is a disease with an orange peel appearance, which occurs as a result of superficial skin edema surrounding the hair follicles[14]. This disease can affect lymph tissue and blood. Gram-positive pathogens, specially Streptococci are treated to control it[11]. 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 disease[11].

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 layer[14]. 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 infection[15].

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 pain[16]. *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 plaques[16]. 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 fluid[16]. 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 center[17].

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 background[17].

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 mirmecia[17].

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 polylobular structure, and a central pore or navel surrounded by crown-shaped peripheral vessels. Transmission occurs through direct contact with infected skin[17]. 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 cytomegalovirus[17].

Fungal Diseases of the Skin

While most fungal infections are superficial, some types of fungi can cause life-threatening infections[18,19,20]. 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 recently[21]. 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 hyperkeratosis[17]. *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 pustules[17]. *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 soles[17]. 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 signs[21]. 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 organisms[21].

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 year[21]. 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 pathways[17].

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 crusting[17]. 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 *Madurella mycetomatis*, *Nigrograna mackinnonii*, *Trematosphaeria grisea*, *Falciformispora senegalensis*, *Scedosporium apiospermum* 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-white[17].

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 presentations[17]. 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 occur[17]. Talaromycosis, talaromycesmar-neffei, 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 ulcers[21].

Parasitic Diseases of the Skin

Epidermal parasitic skin diseases include scabies, pediculosis, cutaneous larva migrans, myiasis, and tungiasis[22,23]. 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 pyogenes[23]. 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[23]. 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[24].

Cutaneous larva migrans (CLM), also called creeping eruption, is a parasitic infestation produced by burrowing the larva of *Ancylostoma braziliense*. The larva enters intact or eroded skin after contact with fecal-contaminated soil. Solitary tracts involving the feet, hands, hips, and genitals are frequently encountered[25]. 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) [26].

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 (log P 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 solubility[27,28]. 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 therapy[8]. On the other hand, polymer-based nanocarriers can easily pass through the hair follicle[29]. Solid-lipid nanoparticles, liposomes, niosomes, microemulsion, nanoemulsion etc. new topical systems are among the frequently used nanocarrier systems[9]. Literature examples of innovative drug delivery systems used in infectious diseases of the skin are summarized in Table 1.

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[30].

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 forming. Solid Lipid Nanoparticles (SLN) are S/Y type emulsions containing solid lipids as oil phase[9].

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.

Table 1: 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 tissue regeneration and biofilm formation[30]
Clindamycin	Nanoparticle	Increased bactericidal activity and acceleration of wound healing[31]
Ionic liquids containing imidazolium cations	Nanoparticle	High antibacterial activity[32]
Antimicrobial peptide LL-37	Cubosome	High antibacterial activity[33]
Gentamicin	Liquid Crystal	Antibiofilm activity sustained for 2 days[34]
Acantho spermumaustrale	Ag Nanoparticle	Higher antimicrobial activity and lower cytotoxicity[35]
Naftifine	Microemulsion	Significant increase in pig skin permeability[36]
Itraconazole	Microemulsion	Higher permeability than skin[37]
Histidine coated silver nanoparticle	Microemulsion	Higher antibacterial activity[38]
Voriconazole/ Sertaconazole	Microemulsion	Absorption from the deeper layers of the skin[39]
Curcumin	Nanoemulsion	Decreases in *C. albicans* growth[40]
Amphotericin B	Nanoemulsion gel	Effective and safe localized release against fungal infection[41]
Essentialoil of *Stenachaeniumme gapotamicum*	Nanoemulsion	Significantly reduced minimum inhibitory concentration and minimum fungicide concentration[42]
Chalcone Acyclovir	Nanoemulsion Organogel	Tendency to accumulate in epidermis and dermis[43] High gelling property with good stability[44]
Amphotericin B	Liposome	Potent and dose-dependent *in vivo* activity against cutaneous leishmaniasis due to high drug accumulation[45]
Azithromycin	Liposome	Success in the treatment of cutaneous leishmaniasis due to its prolonged release ability[46]
Tolnaftate	Liposomal gel	Higher permeability and cure rate[47]
Curcumin	Liposome	More effective anti-inflammatory and antibacterial activities[48]
Fluconazole	Nanofiber	Fungi are susceptible to drug-laden samples[49]
Nisin	Nanofiber	Ability to inhibit the growth of *S. aureus* strains over a long period of time[50]
Amphotericin B	Nanofiber	Significant antifungal activity against eight fungal species[51]
Vancomycin	Nanofiber	High drug retention efficiency and superior antibacterial activity[52]
Acyclovir	Nanofiber	HSV lesions had no significant effect on healing or crusting time[28]
Chlorhexidine	Micelle	Effective antibacterial activity against MRSA[53]
Quaternaryammonium salt	Micelle	Complete recovery with good antibacterial activity and fewer inflammatory cells[54]
Ketoconazole	Micelle	Increased antifungal activity with increased accumulation in the skin and increased drug concentration[55]
Clotrimazole, Econazole nitrate, and Fluconazole	Micelle	Increased skin accumulation for econazole nitrate[56]
Fluconazole	Niosome	Long lasting localized and sustained effec[9]
Eberconazole nitrate	Microsponge	Higher antifungal potential compared to commercial creams[57]
Nitroimidazole compound	Polymeric film-forming system	High concentration in the skin but ineffective in the treatment of cutaneous leishmaniasis[58]

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[31].

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. Mannose-linked and AmB-encapsulated PLGA nanoparticles showed specific targeting on macrophage receptors, thus increasing the efficacy of the drug[32].

Metal Nanoparticles

It is a cluster of small metal atoms with a size range of 10-100 nm. 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%. 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.

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. In the study of Boge *et al*.,[33], the use of cubosomes for topical delivery of antimicrobial peptide (AMP) LL-37 was investigated. 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. 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.

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 microemulsions[65].

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 SC[9].

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. 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. 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. 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.

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. During the preparation of NE, a suitable emulsifier or emulsifier combination is added to achieve long-term stability.

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. 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. Danielli *et al*.,[42] analyzed the chemical composition of the essential oil of *Stenachaenium megapotamicum* 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*. 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.

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.

Liposomes

In 1965, Bangham 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. Potential instability issues of liposomes typically relate to oxidation and/or hydrolysis of lipids, drug leakage, aggregate formation, and liposomal fusion[45]. 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. 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. Ternullo *et al*.,[48] developed an effective liposomal formulation intended for transdermal delivery of curcumin for the treatment of inflamed and infected wounds.

Nanofibers

Nanofibers are nanostructured carriers composed of natural or/and synthetic polymers with a diameter generally less than 100 nm and high specific surface area. 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*. 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. 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 a study conducted at Isfahan University of Medical Sciences[28], 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[53].

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 hydrophobic segment can be made from polyesters such as poly(propylene oxide) or poly(ε-caprolactone) or polymers and copolymers of glycolic and lactic acids[54-55]. 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). 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. 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.

Deng *et al*.,[55] prepared ketoconazole with loaded Y-shaped monomethoxy poly(ethylene glycol)-block-poly(ε-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.

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. Niosomes have proven to be an effective system for antifungal drugs[22].

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. 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 fluconazole[9]. 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

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.

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. 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[59].

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[9].

CONCLUSIONS

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.

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AUTHOR'S CONTRIBUTION

Türkmen A: writing original draft, conceptualization. **Esentürk-Güzel İ:** methodology, formal analysis, conceptualization. **Kara BA:** data curation, investigation. The final manuscript was read and approved by all authors.

DATA AVAILABILITY

The datasets generated during this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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