Mupirocin in Bacterial Skin and Soft Tissue Infection

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Contributor: Preeti Kush

Skin and soft tissue infections (SSTIs) have increased problematically in hospital and ambulatory settings due to the poor immunity of hosts and multidrug-resistant pathogens. Mupirocin (MUP), a global topical antibiotic, is used for the treatment of SSTIs caused by various pathogens due to its unique mechanism of action. However, the therapeutic efficiency of MUP is hampered due to the protein binding and drug resistance caused by frequent use. A combined report covering the various aspects of MUP, such as the synthesis of the novel formulation, loading of the drug, and application against various skin infections, is missing.

skin and soft tissue infections | mupirocin | bacterial infection | drug resistance | novel drug delivery system | magnified delivery

1. Introduction

The skin is the largest organ of the human body, which is daily invaded by various environmental factors such as dryness, cold bites, bacteria, fungi, and accidental fires as well. All these factors may damage skin, leading to skin and skin structure infections (SSIs) or skin and soft tissue infections (SSTIs). These are the most common type of bacterial infection that involves breaching of the integumentary part of the skin (accidental or intentional), ranging from mild severity (pyoderma) to life-threatening (necrotizing fasciitis) incidences [1][2][3]. In recent decades, the incidence rate of SSTIs has increased problematically in hospital and ambulatory settings in the United States due to the poor immunity of the population affected and the multidrug resistance in pathogens [4][5][6]. Traditionally, *Staphylococcus aureus (S. aureus)* and *Streptococcus pyogenes* (group A β-hemolytic streptococci, *S. pyogenes*) were the main culprits for the SSTIs, but, recently, either methicillin-resistant *S. aureus* (MRSA) or macrolide-resistant *S. pyogenes* or both in combination are the main cause of these infections [7]. SSTIs are classified in various forms based on the infection location, progression rate, clinical symptoms, causative agent, extension depth, and severity [1][7][8][9]. In 1998, the United States Food and Drug Administration (USFDA) categorized SSTIs into complicated and uncomplicated treatment. To explain further, complicated treatment addresses deeper tissue infection and requires surgical treatment and uncomplicated treatments are to cure superficial infections. However, this classification did not categorize the patients who were recovering from these infections [10]. Therefore, in 2013, the USFDA adopted a new guideline for pharmaceutical industries and classified all SSTIs into a consolidated term: acute bacterial skin and skin structure infections (ABSSSI) [2]. ABSSSI is defined as a skin bacterial infection with a lesion size of 75 cm^2 area (measured by area of redness, edema, or induration), including bacterial cellulitis/erysipelas, wound infection, and cutaneous abscess [3]. This guideline excludes impetigo, minor cutaneous

abscess, diabetic foot infections (DFI), infection from human or animal bites, decubitus ulcer infection, myonecrosis, necrotizing fasciitis, ecthyma gangrenosum, and chronic wound infections [10][11]. In 2014, the Infectious Diseases Society of America (IDSA) proposed a more relevant and practical classification of SSTIs [12]. The IDSA classified SSTIs based on "(i) skin extension, complicated infection (deep structures of the skin) and uncomplicated (superficial infections); (ii) rate of progression, acute and chronic wound infections; (iii) tissue necrosis, necrotizing and not necrotizing infections" [11]. All the classifications include the patients who possess various clinical manifestations such as cellulitis/erysipelas, wound infection, and major cutaneous abscess, etc. (**Table 1**) [6]. Moreover, these may be categorized into primary (bullous impetigo, cellulitis, carbuncles, furuncles impetigo contagiosa, and folliculitis), and secondary SSTIs (atopic dermatitis, prurigo, contact dermatitis, and neurodermatitis) [9].

Table 1. Descriptive details of various skin and soft tissue infections.

SSTIs	Infection	Pathogen	Description	Ref.
Non-purulent SSTIs	Impetigo	*Staphylococcus aureus, Streptococcus pyogenes*	Superficial infection developed via direct or indirect invasion of bacteria. It is the most common infection in children and presents in two forms, i.e., bullous and non-bullous impetigo.	[7] [9] [13]
	Cellulitis	*Staphylococcus aureus,* beta-hemolytic streptococci (groups A, B, C, or G)	Subcutaneous infections are accompanied by lymphadenopathy and lymphangitis. It is characterized by redness, edema, or induration and usually affects lower limbs.	[7]
	Erysipelas	*Staphylococcus aureus, Streptococcus pyogenes*	Superficial lymphatics and upper dermis infection, usually affects the face and sometimes lower limbs. It possesses well-defined sharp raised borders in contrast to non-infected areas.	[7] [13]
	Folliculitis	*Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes*	It is a superficial inflammation of hair follicles, mainly affecting moist skin with hair.	[7] [9] [14]
Purulent SSTIs	Furuncle	*Staphylococcus aureus*	Furuncle or boil is a deep inflammatory infection developed from folliculitis. Initially, it is a firm, tender, erythematous nodule that becomes fluctuant and painful. It usually infects the face, buttocks, and axillae.	[9] [13]
	Carbuncle	*Staphylococcus aureus, Streptococcus pyogenes*	It is an aggregation of multiple furuncles, involves infection of the hair follicle, and is further extended to subcutaneous tissues. The infection is	[7] [9] [13]

SSTIs	Infection	Pathogen	Description	Ref.
			painful and tender but the patient is well. It is usually observed at the neck, back, and thighs.	
	Abscess	*Staphylococcus aureus, Streptococcus pyogenes,* Streptococcus milleri, viridans, streptococci, coagulase–staphylococci	Focal collection of pus in dermis and hypodermis, characterized by tender, red nodules surrounded by erythematous swelling.	[7] [9] [15] [16]
Complex SSTIs	Burn wound	Anaerobes	Burn wound infection possesses a high bacteria concentration (>10^5 colonies forming unit). It arises immediately after the injury due to the damage of the cutaneous barrier and adaptive immunity. The surrounding tissues of the burn wound exhibit warmth, tenderness, induration, and erythema.	[6] [17]
	Surgical site infection	*Escherichia coli*	It usually arises 4 days after surgery and is categorized into superficial incisional, deep incisional, and organ or space infection. It is diagnosed by incisional discharge, swelling, tenderness, and erythema.	[18]
Diabetic foot infection		*Staphylococcus aureus,* Enterococci, *Pseudomonas aeruginosa, Enterobacteriaceae, Acinetobacter* spp., *Bacteroides* spp.	This infection is most common in diabetic patients and possesses high mortality. This infection encompasses a range from nails to necrotizing limbs. Nails serve as an entry portal for bacterial infection due to poor hygiene.	[6] [19] [20]
Necrotizing SSTIs	Monomicrobial, Polymicrobial	*Staphylococcus aureus, Streptococcus pyogenes* Gram-negatives, *Clostridium* species, Anaerobic bacteria	Necrosis of soft tissues or muscles is initially characterized by erythema and induration with pain followed by skin color change to blue/purple. The patient suffers from systemic toxicity, multi-organ failure, and hemodynamic instability.	[6] [7] [9]
Bite wounds	Human and animal bite	*Eikenella corrodens, Pasteurella multocida, Pasteurella canis, Capnocytophaga canimorsus, Staphylococcus aureus*	It usually arises after biting.	[7] [21] [22]

ctum, and mplicated SSTIs. Optimal management initially comprises physical examination followed by identification of pathogen via a smear of discharge from the lesions. Further, based on culture and susceptibility results, adequate antibacterial therapy should be implemented [19]. Topical antibiotics are an extensively used therapy for the management of SSTIs due to their capability to provide higher concentration to the target area with minimized adverse effects. Additionally, the topical application offers various advantages in contrast to systemic administration, such as patient

compliance and regular inspection of infection, and allows the use of such therapeutic agents (bacitracin or neomycin) that can not be systematically administered. Clinically, various topical antibiotics, such as bacitracin, neomycin, polymyxin B, fusidic acid, and mupirocin (MUP), are currently used for the treatment of SSTIs [23].

MUP is one of the widely used topical antibiotics that is effectively used to treat superficial skin infections caused by Gram-positive and Gram-negative bacteria, especially nasal MRSA due to its broad antibacterial spectrum [23][24][25] and antibiofilm property [18][26]. Commercially, MUP (2%) is available as cream and ointments (Bactroban, Bactoderm, Mupirocin, Turixin) [24]. Due to the unique mechanism of action, it does not possess any cross-resistance with other antibiotics, leading to global use in various hospital departments. However, the potential efficacy of MUP is hampered due to its short half-life (<30 min), high protein binding, and different resistance rates (1–81%) [23][24][27]. Furthermore, the conventional formulations possess some adverse effects such as burning, dryness, itching, rashes, redness, nausea, pain, stinging, swelling, or tenderness [18].

2. Novel Strategies to Augment Mupirocin Delivery in Bacterial Skin Infection

Though MUP is used for the treatment of various bacterial skin infections, it possesses certain limitations such as a short half-life, high protein binding, and drug resistance [23][27]. The resistance can be overcome by the controlled use of MUP for the target decolonization, limiting the treatment duration up to 10 days, and not repeating the treatment for up to 30 days minimum. Further, the antibacterial effect of the MUP can be synergized by combining with other agents such as anesthetics, other topical antibiotics, and natural herbs. Thus, various novel drug delivery strategies have been adopted to enhance patient compliance, decrease the resistance, magnify the delivery of mupirocin, and overcome the limitations of conventional formulations. In this section, various novel formulations such as composite biomaterials/scaffold, hydrogel dressings, liposomes, liposomal hydrogel, microparticles/microspheres, microsponges, nanocapsules, nanofibers, topical sprays, nanostructured lipid carriers, and silicone-based adhesive patches, etc., will be discussed (**Table 2**).

Table 2. Various mupirocin-loaded drug delivery systems for the treatment of skin and soft tissue infections.

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
Composite biomaterials/scaffold	Wound healing	*Staphylococcus aureus, Bacillus subtilis, Escherichia coli*	Collagen, Silica	The collagen scaffolds exhibited more therapeutic potential for the treatment of wound infection and displayed a promising carrier approach for tissue engineering.	[28]
				The developed bio-composite	[29]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				exhibited enhanced water uptake, sustained release, and antimicrobial activity. In vivo results stipulated that the biomaterial showed enhanced adhesion and wound contraction rate, supported by histopathological analysis.	
Hydrogel dressings	Wound healing	*Escherichia coli* (ATCC 8739), *Enterococcus hirae* (ATCC 10541), *S. aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 27853), *Bacillus cereus* (ATCC 7064), *Klebsiella pneumonia*	Chitosan, sodium alginate, carbopol	The developed composite film accelerated the regeneration of the epidermal layer in contrast to the marketed commercial formulation.	[30]
	Diabetic wound		Polyvinyl alcohol	The developed gel was effective for the treatment of diabetic wound and accelerated the wound closure.	[31]
	Primary and secondary	Gram-positive and Gram-negative bacteria	Chitosan	The prepared polymeric membrane was spherical, stable, and elastic, along with having the controlled release property. Furthermore, the membrane exhibited magnified retention of the drug in the skin	[32]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				without any irritation.	
	Surgical wound	*Staphylococcus aureus*	Chitosan	The formulated spherical membrane exhibited superior adhesion and elasticity along with progressive drug release. The Draize patch test revealed that the developed membrane was non-irritant to the skin, along with having magnified antimicrobial efficiency and enhanced retention to the skin.	[33]
	Skin injuries		Acrylic acid	The developed patches exhibited good elasticity and tensile strength, along with enhanced permeation and retention into the skin. The patches were non-irritant to the skin, evidenced by the Draize patch test.	[34]
Liposomes		Methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*	Hydrogenated soy phosphatidylcholine, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (PEG)-2000], cholesterol	Mupirocin was administered intravenously the first time with a distinctive mechanism of action that resulted in a better approach for the treatment of resistant bacterial infection. Further, the results stipulated that	[35] [36] [37]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				nano-mupirocin extended the topical application of mupirocin to the systemic application for the treatment of MRSA infections by changing the pharmacodynamics of mupirocin.	
Liposomal hydrogel	Burn therapy	*Staphylococcus aureus* and *Bacillus subtilis*	Chitosan	Mupirocin-loaded liposomal hydrogel system exhibited prolonged release and superior bio-adhesiveness in contrast to the marketed formulation of mupirocin. In vitro and in vivo studies stipulated that the developed system was significantly safe, more therapeutically active along with shorter healing time, and exhibited antibiofilm activity against the bacterial pathogen.	[38] [39]
Microparticles/Microspheres	Wound healing	*Staphylococcus aureus*	Eudragit	The developed formulation exhibited the sustained release of mupirocin along with magnified storage. The morphology, drug release, and antimicrobial activity of the developed formulation were dependent on the drug loading and the solvent. Time-	[40] [41]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				kill assay results revealed that there was no loss of the antimicrobial activity of mupirocin during the encapsulation.	
Microsponges	Surgical wound	*Staphylococcus aureus*	Ethylcellulose	Mupirocin microsponge exhibited a diffusion-controlled release profile along with ~5 times magnified retention on rat skin in contrast to the marketed formulation. The formulation was found stable and non-irritant, evidenced by the Draize patch test.	[42]
	Wound healing	*Staphylococcus aureus, Escherichia coli*	Keratin, fibrin, and gelatin	The developed formulation exhibited a prolonged release pattern along with enhanced biocompatibility and cell adhesion properties. The antimicrobial activity results demonstrated that the mupirocin-loaded sponge was a promising medicated dressing material for the treatment of wound infection.	[43]
Nanocapsule/nanoparticles	Wound healing		Poly(ε-caprolactone)	The developed nanocapsules showed excellent stability at 40 °C and room temperature.	[44]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
		Methicillin-resistant *Staphylococcus aureus* (MRSA)	Chitosan, selenium	The tailored formulation showed remarkable therapeutic potential in terms of diabetic wound healing and wound contraction compared to the native mupirocin.	[45]
		Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, and *Escherichia coli*	Poly(ethylene oxide)–poly (propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO)	The tailored formulation exhibited reduced minimum inhibitory concentrations and minimum bactericidal concentrations against *S. aureus, S. epidermidis, Pseudomonas aeruginosa,* and *E. coli* compared to the mupirocin ointment. Further, the developed formulation was safe, effective, and biocompatible for the treatment of wound infection.	[46] [47]
Nanofibers	Wound healing	*Staphylococcus aureus*	Poly-l-lactic acid	The tailored scaffold exhibited a different release profile for both drugs, suggesting that the release kinetics of one drug was altered by keeping the two different drugs in the same polymer matrix. The dual drug scaffold released a significantly higher drug and even compensated the inactive monic acid	[48]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				to act on the applied area, resulting in the maintainence of a sufficient concentration of mupirocin in the infected wound for more than a 72 h period, resulting in profound wound healing.	
	Burn wound	*Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli*	Polyurethane	The developed fiber mat was enough for wound hydration via providing adequate environmental humidity. Moreover, the tailored nanofiber exhibited sufficient cell spreading and attachment. The cytotoxicity results revealed that the antibacterial activity of the scaffold was increased proportionally with the increase in mupirocin concentration (2–5%). Further, the histopathological study revealed that the nanofibrous mat was enough for burn wound healing due to negligible inflammation.	[49]
		Staphylococcus aureus, Pseudomonas aeruginosa, and *Escherichia coli*	Polycaprolactone	The tailored multifunctional double-layer nanofibrous scaffold (MDLS) was effective for	[50]

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
				the management of wound infection, along with superior tensile strength with enhanced contact angle and swelling ratio. Furthermore, cytotoxicity results revealed that the MDLS was more biocompatible due to the addition of chitosan in contrast to polycaprolactone nanofibers.	
		Staphylococcus aureus, and *Escherichia coli*	Keratin, and coenzyme Q10, and polyvinyl alcohol	The tailored formulations were biocompatible, evidenced by the skin irritancy test. Further, the therapeutic efficacy of the tailored formulation was assessed by antimicrobial activity against various strains of *S. aureus* (2583, 2586, 2587, 2590), MRSA 2555, and *E. coli* 1808. Moreover, cell proliferation results evidenced the ability of nanofibers to support the keratinocytes' growth due to the presence of coenzyme Q10.	[51]
Topical spray	Burn wound	*Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia*	Eudragit E100	The developed spray exhibited magnified antimicrobial activity (18-fold) against *S. suis*, in	[18] [52]

ng to its unique mechanism of action; however, the therapeutic efficacy is hampered due to resistance, poor half-life, and protein binding. The therapeutic efficacy of MUP can be augmented by combining with other agents and using a suitable biocompatible carrier that promotes and support cell viability and cell proliferation together with sustained release of MUP. The sustained and progressive release of MUP from the novel carrier can maintain the drug

Drug Delivery System	Infection	Pathogen	Biomaterial	Outcome	Ref.
		coli, and *Streptococcus suis (S. suis)*		contrast to the marketed formulation due to close contact between spray and skin, leading to the formation of a thin film on the infected surface. Moreover, the topical formulation was found non-irritant to the human skin without any toxicity to the monocytes, keratinocytes, and fibroblasts cells. Additionally, the safety profile of the formulation was also confirmed by zero production of nitric oxide and inflammatory cytokines (IL-1b and TNF-a) due to its antiendotoxin effect.	
Nanostructured lipid carrier			Cetyl palmitate, caprylic acid	Nanostructured lipid carrier (NLC) reduced the metabolic degradation of MUP via the protective lipid layer of NLC which resulted in a 40-fold and 55-fold area under the curve and half-life, respectively, in contrast to native MUP.	[53]

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