



REVIEW ARTICLE

FROM CONVENTIONAL OINTMENTS TO NANOEMULSION SYSTEMS: TRANSFORMING TOPICAL MUPIROCIN DELIVERY FOR IMPROVED ANTIBACTERIAL OUTCOMES

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ABSTRACT: Mupirocin is a topical antibiotic that is commonly used for the treatment of superficial skin infections due to Gram-positive bacteria such as *Staphylococcus aureus*, and methicillin-resistant *S. aureus* (MRSA). Traditional ointments and creams can however have drawbacks in terms of skin penetration, follicular drug delivery, chemical stability and effectiveness against bacterial biofilms. The nanoemulsions and nanoemulgels as an improvement of topical delivery of mupirocin, antibacterial activity and wound healing are discussed in this review. Literature was reviewed on formulation development, excipient selection, the methods of preparation, skin permeation, antibacterial activity, disruption of bacteria associated with biofilms, stability, biocompatibility and regulatory aspects. Nanoemulsions are lipid-based delivery systems in which the droplets are of nanoscale dimensions and might increase the solubility of the drug, increase the contact with the skin and increase the deposition into the skin and in the hair follicles. Additives such as non-ionic surfactant, cosurfactant and certain lipid ingredients could enhance the formulation properties and drug release, meanwhile, suitable gelling agents can increase formulation viscosity, extend skin dwelling time and facilitate the application of the formulation. The literature reviewed indicated that there were promising pre-clinical results of enhanced skin permeation and retention, improved antibacterial activity against MRSA and potential benefits in biofilm management and wound repair. However, these results will vary with formulation formulations, experimental conditions and the biological models used. There are still key points to consider for clinical translation, such as long-term stability, excipient safety, manufacturing reproducibility and regulatory requirements. In conclusion, the mupirocin loaded nanoemulsions and nanoemulgels are effective means to conquer some of the selected limitations of conventional topical formulations. There is a need for additional standardized investigations, thorough safety evaluations and carefully planned clinical trials to demonstrate their therapeutic benefits and clinical utility.

Keywords: Mupirocin, Nanoemulsions, Topical Drug Delivery, Methicillin-Resistant *Staphylococcus aureus* (MRSA), Bacterial Biofilms

I. INTRODUCTION

Mupirocin, also known as pseudomonic acid A, is a naturally-occurring antibiotic metabolite that is biosynthesized via a complicated polyketide synthase pathway by the soil bacterium *Pseudomonas fluorescens* (NCIMB 10586) [1]. Mupirocin is structurally a novel antibiotic molecule consisting of a monic acid core, linked to a final aliphatic side chain of 9-hydroxynonanoic acid [2]. Monic acid has a substituted tetrahydropyran ring with an attached oxirane (epoxide) ring, which is also stereospecific with hydroxyl functions that control its biological activity and molecular receptor interactions [2]. The mechanism of action of mupirocin is selective, and involves reversible competitive inhibition of bacterial isoleucyl-tRNA synthetase (IleRS) [2, 3]. In the process of protein biosynthesis, IleRS catalyzes the activation of isoleucine and charging of the cognate tRNA molecule, which is a basic reaction that consumes adenosine triphosphate (ATP). The isoleucyl-adenylate reaction intermediate is structurally similar to the monic acid moiety of

mupirocin, resulting in the binding of mupirocin to the catalytic pocket of bacterial IleRS with high affinity (inhibition constant, $K_i \approx 2.5-10$ nM) [4, 5]. This interplay is competitive against endogenous L-isoleucine, inhibits protein synthesis of bacteria, induces the stringent response and ultimately the growth of bacteria is arrested in a concentration-dependent fashion [6]. The active site of mammalian isoleucyl-tRNA synthetase is structurally different from that of its bacterial counterpart, and has only about 1,000-8,000-fold lower affinity for mupirocin [7]. The therapeutic safety of topical mupirocin is in part due to this enzymatic selectivity. Systemic administration is associated, however, with rapid inactivation of the compound due to the labile ester linkage being cleaved from the plasma and hepatic carboxylesterases leaving the compound inactive for biological activity [8, 9]. Therefore, mupirocin is mainly prescribed topically for treatment of Gram-positive bacterial infections of the mucocutaneous surfaces and skin caused by susceptible bacteria [8, 9].

Mupirocin is commonly used in clinical practice to treat superficial bacterial skin infections and for some decolonization protocols [9, 10]. Topical mupirocin 2% is indicated for infections of the skin like impetigo, superficial ecthyma, sycosis barbae, acute folliculitis and secondarily infected traumatic skin lesions. Topical mupirocin has been shown to be clinically and microbiologically successful in clinical studies of impetigo patients with the aim of localizing bacterial infections [10]. Another major application is the decolonization of methicillin-resistant *Staphylococcus aureus* (MRSA) in a few specific patients in hospital settings, healthcare workers and surgical candidates prior to surgery [11]. Anterior nares are an important reservoir for *S. aureus* colonization, a source that can be associated with healthcare-associated infections, such as surgical-site infections. Intranasal 2% mupirocin ointment is a standard decolonization therapy that is used twice daily for 5 consecutive days and sometimes in combination with other infection-prevention therapies [11].

Although clinically useful, bacterial resistance is a problem with mupirocin [12]. There are two levels of mupirocin resistance: low level and high level. Low-level resistance is linked to MICs of 8-64 µg/mL and is generally caused by mutations in the chromosomal *ileS* gene that change the mupirocin-binding site of bacterial IleRS [12]. High-level resistance on the other hand, is usually accompanied by significantly higher MICs (typically ≥512 µg/mL) and is frequently due to such acquired resistance genes as *mupA* (*ileS2*) which encodes an isoleucyl-tRNA synthetase that is less susceptible to mupirocin [12]. The resistance mechanisms point to the necessity of exploring formulation strategies to enhance the local anti-bacterial activity and drug delivery of these formulations. Traditional ointments and creams may lack penetration into skin, be poorly deposited in follicles, be unstable in the presence of bacteria growing in biofilms, and be poorly delivered to the bacteria growing in the biofilms. As such, interest has been generated in the possibility of using lipid-based nanoemulsions and nanoemulgels as topical drug delivery systems. The nanoscale droplets, appropriate lipid components, surfactants, and possibly gelling agents could enhance the solubilization of drugs, skin contact, retention, and penetration into the skin and hair follicles. These properties offer the basis to explore the possibility of using mupirocin nanoemulsions as alternative formulations to enhance topical delivery and antibacterial activity, but their clinical benefits and potential for tackling resistant infections need to be systematically investigated [12, 13].

2. Conventional Formulations and Inherent Bottlenecks

2.1 Commercial Landscape: Ointments vs. Creams

Clinical use of mupirocin has been 30+ years old, using 2% mupirocin free acid ointment in a water soluble polyethylene glycol (PEG 400 and PEG 3350 blend) base (Bactroban® Ointment) and a 2% mupirocin calcium cream in an oil-in-water emulsion base (Bactroban® Cream) [14, 15]. Both formulations exhibit high potency against planktonic cells on agar plates, but both vehicles are severely deficient in terms of

physicochemical and biopharmaceutical characteristics in real clinical situations, such as exuding and necrotic dermatological lesions (Table 1) [14, 15].

2.2 Stratum Corneum Barrier and Sub-Therapeutic Deposition

At the outer surface, the epidermis (SC) forms a formidable physicochemical barrier of anucleated keratin-packed corneocytes in continuous lamellar lipid bilayers that are composed mainly of ceramides, cholesterol and long-chain free fatty acids [16, 17]. PEG is extremely polar and hydrophilic, and thus is not thermodynamically able to partition into or disrupt these intercellular lipid lamellae that are lipophilic [17, 18]. To this end, quantitative skin distribution studies have shown that more than 90-95% of topically applied mupirocin stays in the superficial layers of the non-viable corneocytes [16, 17]. Only 2–3% of the applied dose successfully penetrates the viable epidermis and dermis to treat deep pyoderms, cutaneous abscesses and invasive pathogens [17, 18].

Table 1: Conventional 2% Mupirocin Ointment vs. Nanoemulsion Systems

Parameter	Conventional 2% Ointment	Mupirocin Nanoemulsion / Nanoemulgel	Clinical Impact
Vehicle Base	Hydrophilic PEG 400 / 3350 blend [14].	Biocompatible sub-micron o/w dispersion in polymer gel.	Eliminates PEG toxicity; non-irritating matrix.
Droplet Size	Macroscopic coarse particles (>10–50 µm).	Nanometric droplets (20–150 nm; PDI < 0.25).	High specific surface area accelerates interfacial flux.
SC Permeation	>95% trapped on superficial SC [16, 17].	Enhanced <i>via</i> transient intercellular lipid fluidization.	High antibiotic delivery to viable epidermis/dermis.
Follicular Depot	Bypasses sebum-rich hair follicles.	Selective transfollicular channeling and depot formation.	Eradicates deep follicular <i>S. aureus</i> colonies.
Biofilm Action	Impassable; cannot penetrate anionic EPS [19, 20].	Navigates hydration pores; disrupts EPS scaffolding.	80–98% biofilm clearance; persister eradication [21, 22].
Toxicity Risk	Nephrotoxic risk from absorbed PEG on burns [23, 24].	Zero vehicle toxicity; GRAS lipids and biopolymers.	Safe on extensive burns and renal patients.
Stability	Rapid ester hydrolysis in wound moisture [25].	Lipid core shields labile ester bond from hydrolysis.	Prolongs shelf-life and active wound concentrations.
Synergy	Zero intrinsic antibacterial activity.	Bioactive oils (eucalyptus, tea tree) provide dual action.	Reduces MRSA MIC 2- to 8-fold.
Rheology	Greasy, sticky, stains, melts at skin temp.	Shear-thinning, non-greasy, bio-adhesive gel.	Improves compliance and wound contact time.
Resistance Risk	High; sub-inhibitory gradients drive <i>mupA</i> [12, 13].	Supra-MPC concentrations suppress resistance window.	Prevents emergence and transfer of resistance.

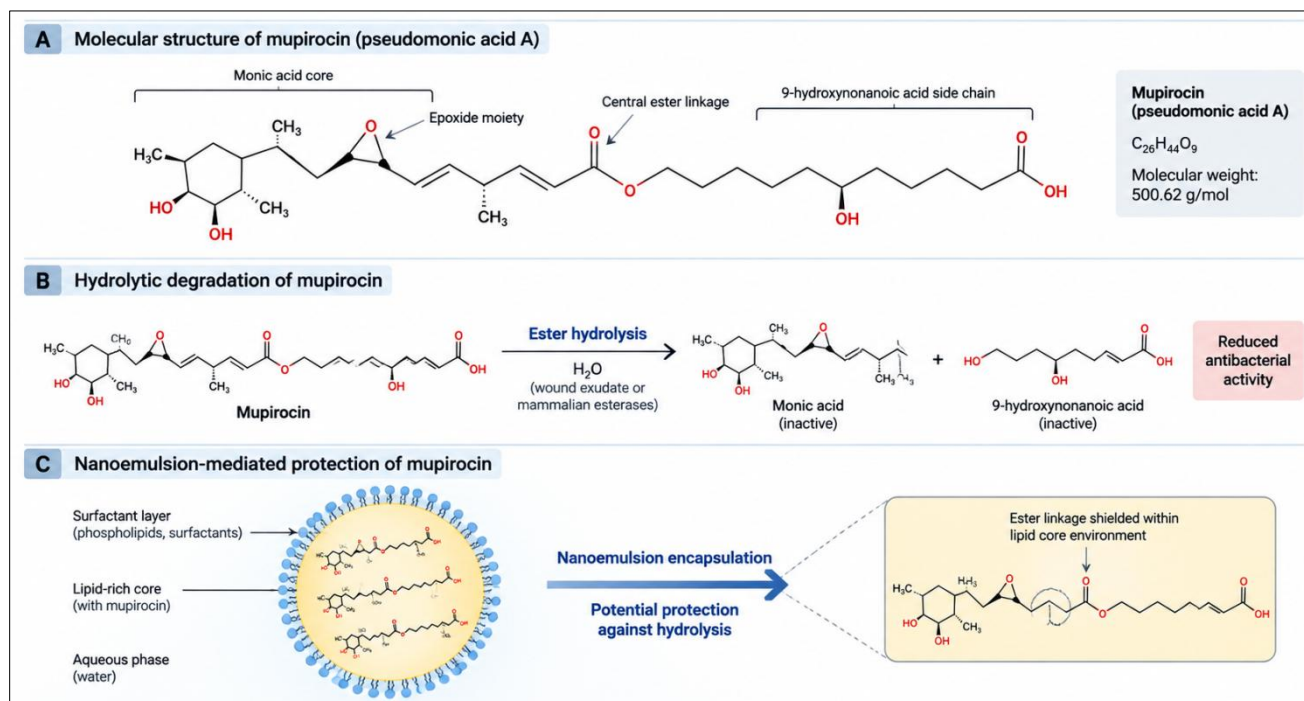


Figure 1: Chemical Structure of Mupirocin and Mechanisms of Inactivation

In addition, the hydrophilic PEG vehicles are not suitable to penetrate lipid-rich sebum inside pilosebaceous units [17, 18]. The follicular infundibulum is an ecological niche for chronic colonization by *S. aureus*, and it is a key role in the pathogenesis of recurrent folliculitis, hidradenitis suppurativa and furunculosis. The lack of therapeutic payloads reaching deep hair follicle bacterial colonies causes clinical recurrence and treatment failure with conventional PEG ointments [17, 18].

2.3 The Biofilm Dilemma in Chronic Wounds

Chronic, non-healing wounds (diabetic foot ulcers, venous stasis ulcers, pressure necrosis, and infected thermal burns) typically have surface-adherent, dense biofilms populated mainly by pathogens [19, 20]. These biofilms are surrounded by a self-produced extracellular polymeric substance (EPS) matrix, which contains exopolysaccharides (e.g., poly-N-acetylglucosamine), extracellular DNA (eDNA) and structural proteins that have a negative charge [19, 20]. The EPS matrix is viscous and negatively charged and prevents the entry of polar formulations, thus reducing the antibiotic activity of mupirocin by 100- to 1,000-fold for EPS-producing bacteria compared to planktonic bacteria [20, 21].

In addition, mature biofilms undergo phenotypic differentiation into metabolically-quiescent persister cells under conditions of nutrient and oxygen limitation in the core of the deep hypoxic region of the biofilm [21, 22]. Persister cells are inherently resistant to sub-inhibitory concentrations of mupirocin that can be achieved with the use of conventional ointments and represent a persistent source of recurrent infection when treated with mupirocin [21, 22].

2.4 Systemic PEG Toxicity and Chemical Instability

Systemic polyethylene glycol toxicity is a serious clinical problem with conventional mupirocin ointment [23, 24]. Low-molecular-weight PEG 400 is easily absorbed through the damaged barriers of the skin and other wounds into the systemic circulation of patients with extensive partial or full thickness burns or denuded wounds. Absorbed PEG oligomers are excreted by the kidneys and may cause severe hyperosmolality, high-anion-gap metabolic acidosis and acute renal tubular necrosis [23, 24]. Strict boxed warnings against use of PEG-based mupirocin ointments are required by FDA in case of moderate to severe renal impairment and patients with extensive open wounds [14]. Moreover, the central ester bond of mupirocin is easily hydrolyzed in exudative, moist wound conditions to produce inactive monic acid and 9-hydroxynonanoic acid (Fig. 1) [25]. Low bioadhesion, formulation melting at skin temperature and greasy texture are also factors that diminish patient compliance [25].

3. Engineering Nanoemulsions for Mupirocin Delivery

3.1 Structural Principles and Thermodynamic Stability

The nanoemulsions are kinetically stable, non-equilibrium colloidal dispersions that are formed by the presence of an interfacial film of surfactant(s) and co-surfactants, which stabilize droplets of oil and water with a mean diameter of 20-200nm [26, 27]. Nanoemulsions are thermodynamically stable systems that can be prepared with much lower surfactant concentrations (4–12% w/w) and thus reduce the toxicity and irritation on the skin surface compared to microemulsions, which need high surfactant concentrations (20–40% w/w) [26, 28].

Stokes' Law states that the sedimentation or creaming velocity (v) of droplets is proportional to the square of droplet radius (r^2), and the density difference between the droplet (ρ_p) and the suspending fluid (ρ_m), and g is the acceleration due to gravity. The phase separation, flocculation and coalescence are extremely stable in the case of nanoemulsion because the droplet size is sub-micron and, therefore, the Brownian motion dominates over the gravitational separation as a cause of phase separation and coalescence in long storage periods. Oil in water (o/w) nanoemulsions are ideal for topical delivery of mupirocin because they contain a non-greasy, water washable external phase that encases mupirocin into the internal lipid core, which protects the labile ester bond [29, 30, 31].

3.2 Excipient Selection: Lipids, Surfactants, and Bioactive Oils

The solubilization, encapsulation efficiency and chemical stability of mupirocin in the lipid cores are directly determined by the lipid core selection [30, 31]. The medium-chain triglycerides (MCT; Miglyol 812), mono-/diglycerides (Capmul MCM) and long-chain ethyl esters (ethyl oleate) offer a high solubilizing capacity (>25–50 mg/mL) [30, 31]. Bioactive essential oils (such as eucalyptus oil with a high content of 1,8-cineole; tea tree oil with a high content of terpinen-4-ol; and clove oil with a high content of eugenol) are used as functional lipid cores in formulations. These terpenes disrupt bacterial cell membrane and have intrinsic antibacterial activity, which is beneficial in combination with mupirocin against resistant phenotypes of MRSA [32, 33].

The non-ionic surfactant class of materials, such as Polysorbate 80 (Tween 80), Labrasol (caprylocaproyl

polyoxyl-8 glycerides) and Kolliphor EL (polyoxyl 35 castor oil), form flexible and dense interfacial films with low skin irritation potential [34]. Co-surfactants like Transcutol P (diethylene glycol monoethyl ether) lower the interfacial tension to near zero (<2 mN/m), increase the interfacial film curvature, and are very effective chemical penetration enhancers as a result of fluidizing the intercellular lipid bilayers of the stratum corneum [34, 35].

3.3 Fabrication Technologies and Nanoemulgel Formulation

Nanoemulsions can be prepared by two types of methods – high energy methods and low energy methods – such as high-pressure homogenization (800–1200 bar), microfluidization, or high intensity probe ultrasonication (HIPU) and phase inversion temperature (PIT) [36, 37]. Homogenization at high energies yields better control of particle size ($PDI < 0.20$), droplet reproducibility, but requires an active in-line chilling (4–10 °C) to avoid thermal degradation of mupirocin [36, 37].

However, because of low inherent viscosity, liquid nanoemulsions tend to run off when applied externally [38, 39]. Nanoemulsions are converted to a thixotropic nanoemulgels by adding a hydrophilic biopolymer, like Carbopol 940 (0.5–1.0%), chitosan (1.0–2.0%), hyaluronic acid (1.0–1.5%) or Pluronic F-127 [38, 39] to ensure sustained contact with the skin (Table 2). The pseudoplastic shear-thinning, yield stress is ideal for nanoemulgels to be spreadable under shear and stay in place on standing. Physicochemical characterization of the droplets confirms their size of 50–150 nm, low polydispersity index (<0.20), sustained drug release (anomalous non-Fickian diffusion) (>25 mV), and high encapsulation efficiency (>90%) (Fig. 2).

Table 2: Excipients in Topical Mupirocin Nanoemulsions				
Category	Representative Excipients	Conc. (% w/w)	HLB	Mechanistic Role
Lipid Core	Capmul MCM, Miglyol 812, Ethyl Oleate	5.0–20.0%	N/A	Solubilizes mupirocin (>25–50 mg/mL); shields ester bond [30, 31].
Bioactive Oils	Eucalyptus, Tea tree, Clove oil	1.0–8.0%	N/A	Dual-action lipid phase; disrupts bacterial membrane [32, 33].
Surfactants	Tween 80, Labrasol, Cremophor EL	4.0–15.0%	12.0–15.0	Lowers interfacial tension (<2 mN/m); steric barrier [34].
Co-Surfactants	Transcutol P, Propylene glycol	2.0–10.0%	Amphiphilic	Increases film fluidity; enhances SC penetration [34, 35].
Gelling Agents	Carbopol 940, Chitosan, Hyaluronic acid	0.5–2.0%	Polymer	Imparts thixotropic yield stress; prolongs residence [38, 39].
Antioxidants	Alpha-tocopherol (Vit E), BHT	0.02–0.5%	Lipophilic	Prevents lipid peroxidation and mupirocin degradation.

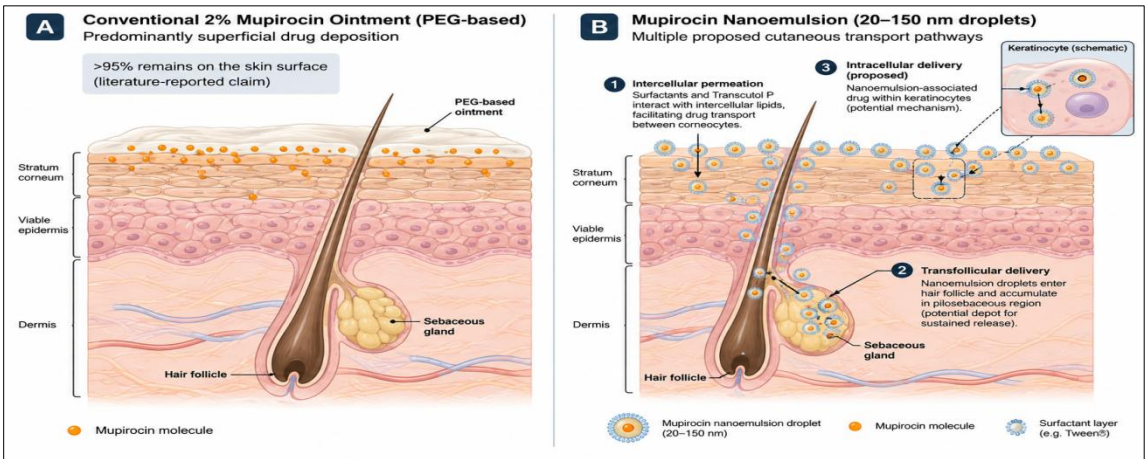


Figure 2: Cutaneous Permeation: Ointment vs. Nanoemulsion

4. Mechanisms of Enhanced Permeation and Cutaneous Transport

4.1 Stratum Corneum Lipid Fluidization and Transfollicular Shunt

Nanoemulsions have been proven to increase the cutaneous transport of drugs using two complementary mechanisms [40, 41]. In the intercellular pathway, non-ionic surfactant (Tween 80, Labrasol) and amphiphilic co-surfactant (Transcutol P) partitioning occurs in the stratum corneum lipid bilayers [40, 41, 42]. The ATR-FTIR results show that these excipients interfere with the acyl chains of ceramide and cause a blue-shift in the symmetric and asymmetric CH₂ stretching vibrations (from 2850/2918 cm⁻¹ to higher frequencies), indicating a change in the packing structure from rigid orthorhombic to disordered liquid crystalline states [40, 42, 47]. Moreover, unsaturated fatty acids (oleic acid) create micro-voids, which help drugs partition rapidly into viable epidermis [40, 42].

At the same time the transfollicular 'shunt' pathway is important [43, 44]. The hair follicles and sebaceous glands penetrate 1,000–3,000 µm through the stratum corneum [44, 45]. Hydrophilic PEG ointments are incapable of being absorbed by lipophilic sebum, whereas sub-micron lipid nanodroplets (50–150 nm) penetrate the orifices of follicles with ease by capillary action and Brownian motion [43, 45, 48]. Nanodroplets interact with sebum, creating an intra-

follicular drug depot that continually releases mupirocin into the surrounding dermal tissue to kill deep follicular colonies of *S. aureus* [43, 45, 48].

4.2 Breathable Semi-Occlusion and Intracellular Pathogen Eradication

The nanoemulsions offer 'breathable semi-occlusion' [46] unlike PEG Ointments which absorb moisture from viable tissues and petrolatum-based ointments which create an impermeable barrier leading to maceration of the skin. The nanodroplet monolayer effectively lowers elevated transepidermal water loss (TEWL) by 30–50%, restores corneocyte water content and enhances tissue diffusivity without compromising physiological gaseous exchange [46, 49].

Moreover, *S. aureus* can avoid extracellular antibiotic therapy by being phagocytosed by the host keratinocytes and macrophages by means of endocytosis with the help of fibronectin binding protein [50, 51]. Traditional mupirocin is not well permeable to the eukaryotic membrane, and therefore does not affect intracellular bacteria (Fig. 3) [50]. However, lipid nanodroplets enter cells via endocytosis, which occurs either by clathrin or caveolae, and are delivered to phagolysosomes to achieve 10-to 20-fold higher intracellular killing than free antibiotic and directly transferring lethal antibiotic levels into cells with infected MRSA [50, 51].

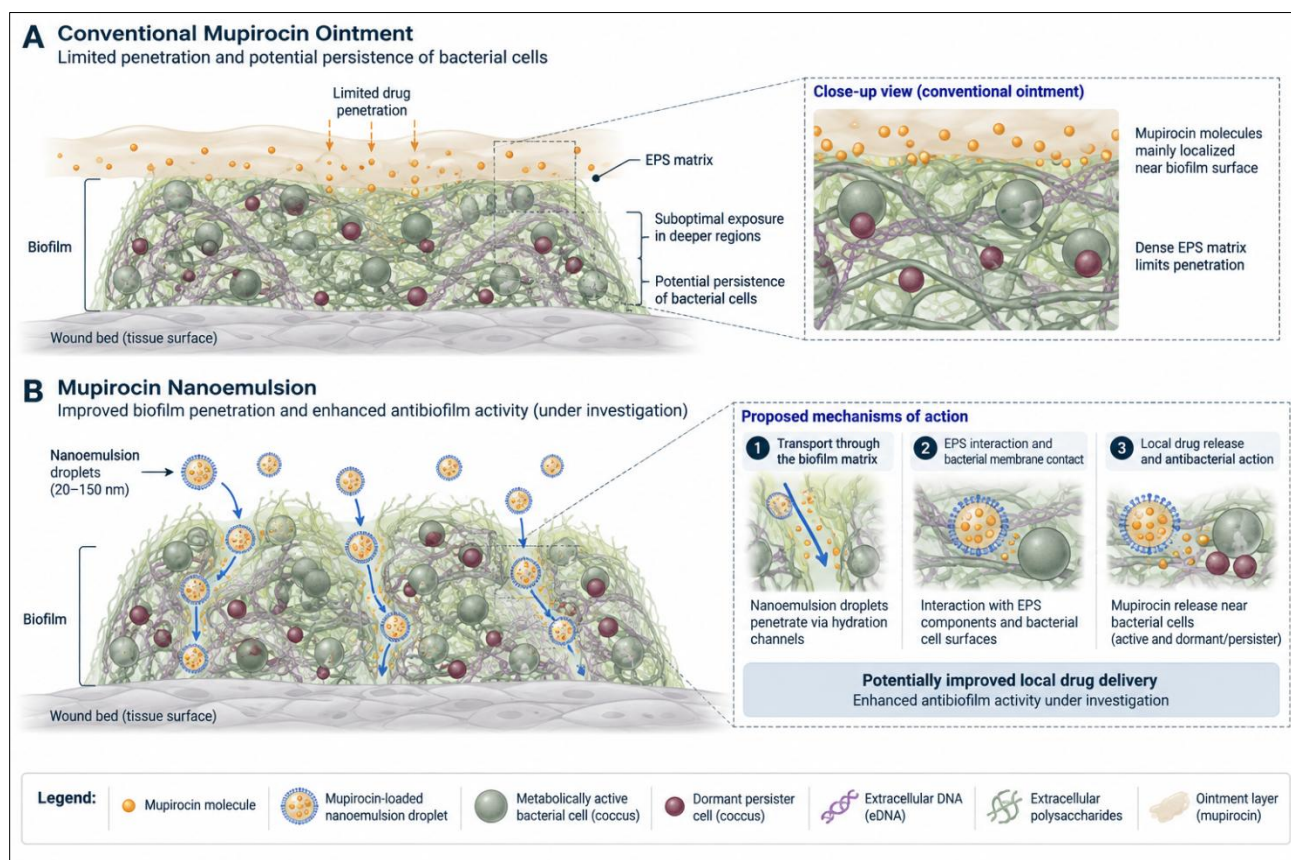


Figure 3: Nanoemulsion-Mediated Biofilm Disruption and Persister Eradication

5. Antibacterial Efficacy and Biofilm Eradication

5.1 In Vitro Potency, Biofilm Disassembly, and Persister Clearance

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of mupirocin is consistently reduced by 2-8 fold against *S. aureus* (MSSA, CA-MRSA, HA-MRSA) and *S. pyogenes* after encapsulation in a nanoemulsion (e.g. MRSA MIC after nanoemulsion is 0.125 µg/mL compared to 0.50 µg/mL for the free drug) [52, 53, 54]. Time-kill assays demonstrate rapid bactericidal activity, with 99.9% of the colony-forming units (CFUs) destroyed in 4–6 hours, and 100% in 8–12 hours [54, 56]. Non-ionic surfactant permeabilizes the bacterial cell envelope to allow mupirocin to have a rapid access to the intracellular IleRS [54, 56].

Nanoemulsion droplets penetrate the interstitial hydration channels of bacterial biofilm and erode components of the lipidic matrix, which also breaks down the structural integrity of EPS, which is embedded in poly-N-acetylglucosamine (PNAG) and eDNA matrices [53, 55] (Figure 1). In comparison with conventional ointment, which only clears 15–25% of mature biofilm biomass, mupirocin nanoemulsions clear 80–98% of mature biofilm biomass [56, 57, 58] by using confocal laser scanning microscopy (CLSM). In addition, nanodroplets can fuse with the membranes of dormant persister cells and release lethal levels of drugs to kill these quiescent phenotypes [58, 59].

5.2 Synergistic Combinations and Resistance Mitigation

The fractional inhibitory concentration index (FICI) for the combinations of mupirocin with bioactive phytotherapeutic agents (eugenol, 1,8-cineole) and biogenic silver nanoparticles (AgNPs) showed strong FICI values in the range of 0.18 to 0.38 (FICI < 0.5 indicate synergy) [54, 58, 59]. Terpenes and silver ions penetrate the outer membrane of the bacteria and create reactive oxygen species that allow mupirocin to enter and exceed the activity of target enzymes [54, 58]. Involving multiple targets broadens the antimicrobial activity to include Gram-negative bacteria like *Pseudomonas aeruginosa* [54, 59].

Conventional ointments provide sub-inhibitory levels in the tissue, which falls within the Mutant Selection Window (MSW) and selects chromosomal ileS point mutations and mupA transfer on the plasmid [12, 13, 60]. By contrast, a number of nanometer-sized particles, known as nanoemulsions, can be concentrated at a site to a level much higher than the mutant prevention concentration (MPC > 500 µg/mL) (Table 3). A >64-fold increase in the MIC for MRSA exposed to free mupirocin was observed after 30 serial passages compared to no change in the MIC after 30 serial passages for MRSA exposed to mupirocin nanoemulsions, showing the effectiveness of the nanoemulsions in closing the mutant selection window for MRSA [54, 60].

Table 3: Summary of Preclinical Studies on Mupirocin Nanoemulsions

System & Vehicle	Key Excipients	Droplet Size & Zeta	Model & Pathogen	Quantitative Outcomes
O/W Nanoemulsion	Capmul MCM, Tween 80, Transcutol P	84.2 nm / -18.4 mV	Human skin ex vivo; MRSA	4-fold MIC reduction; 3.8-fold higher skin retention; non-toxic [54].
Chitosan Nanoemulgel	Oleic acid, Labrasol, 1% Chitosan	112.5 nm / +34.6 mV	MRSA biofilm; Rat wound	94.2% biofilm kill; 98.4% wound closure by Day 12; complete re-epithelialization [66].
Eucalyptus Nanoemulsion	Eucalyptus oil, Tween 20, PEG 400	68.4 nm / -14.2 mV	Porcine skin; CA-MRSA	Synergistic kill (FICI = 0.28); 4.2-fold higher follicular deposition [58].
Carbopol Nanoemulgel	Miglyol 812, Cremophor, 0.75% Carbopol	96.8 nm / -22.1 mV	Rat thermal burn; MRSA	Flux Jss = 18.6 µg/cm²/h (4.4x ointment); zero PEG toxicity; rapid healing [65].
AgNP Hybrid Emulsion	Peceol, Solutol, 15 nm AgNPs	128.0 nm / -28.6 mV	Polymicrobial: MRSA + <i>P. aeruginosa</i>	Broad-spectrum synergy (FICI = 0.22); >90% polymicrobial biofilm eradication [54, 59].
Hyaluronic Nanoemulgel	Capmul MCM, Tween 80, 1.5% HA	92.1 nm / -26.4 mV	Diabetic db/db mice; MRSA	>4.5-log10 CFU reduction; enhanced VEGF/CD31; healed 6 days faster [65, 66].

6. Preclinical In Vitro, Ex Vivo, and In Vivo Evidence

6.1 Ex Vivo Skin Permeation and In Vivo Wound Healing

Mupirocin nanoemulgels show significant superiority over commercial PEG ointment in Franz diffusion cell studies with human and porcine dermatomed skin with a steady-state transdermal flux of Jss = 18.6 ± 1.4 µg/cm²/h (more than 4.4-fold greater than ointment, 4.2 µg/cm²/h) [61, 65]. Differential tape stripping assays reveal strong epidermal and dermal distribution (more than 70–80% of applied mupirocin recovered in the viable epidermal layers versus less than 3% for ointment) and a low amount of mupirocin recovered from transdermal receptors, suggesting that it is not likely to have systemic toxicity and is strongly active in the epidermis and dermis [62, 65, 66]. The *in vivo* studies in MRSA infection full-thickness excisional and burn wound models validate the accelerated tissue regeneration in rats and diabetic (db/db) mice [62, 65, 66]. When applied as a once-daily nanoemulgel,

mupirocin causes >50% wound closure by Day 4–5, >80% by Day 8 and >96–99% re-epithelialization by Day 12–14, whereas the conventional ointment formulates take >18–21 days to achieve re-epithelialization [62, 65, 66]. The reduction in microbial bioburden in wound tissue was >3.5- to 4.5-log10 per gram after 48–72 hours and was sterile by Day 5–7 [65, 66].

6.2 Histopathology, Angiogenesis, and Biocompatibility

Histological analysis (H&E, Masson's trichrome) shows that the wounds heal in a more rapid manner from an inflammatory state to a proliferative stage when treated with nanoemulgel [65, 66]. By Day 7-10 treated tissues show signs of neo-angiogenesis, dense granulation tissue, well organized type I collagen bundles, and a re-established epidermal layer with distinct rete ridges [65, 66]. CD31 and vascular endothelial growth factor (VEGF) are greatly upregulated, while pro-

inflammatory cytokines (TNF-alpha, IL-1beta) are down-regulated, and transforming growth factor beta1 (TGF-beta1) is up-regulated, by immunohistochemistry [65, 66].

OECD 404 Draize rabbit skin irritation tests have been completed and show a Primary Irritation Index (PII) of 0.00 / 8.00 (classified as completely non-irritating) [63]. Human dermal fibroblasts (HDF) and HaCaT keratinocytes have been used in in vitro cell viability studies and have exhibited >85–95% viability when exposed to concentrations 50 fold higher than their MIC [65, 66]. The results of hemolysis test of erythrocytes were under the limit of 5% set by ASTM F756-17 [64] indicating excellent hemocompatibility and safety for open wound applications.

7. Industrial, Regulatory, and Translation Perspectives

7.1 Stability Optimization and Industrial Scalability

To achieve the physical and chemical stability of mupirocin nanoemulsions under ICH Q1A(R2) conditions, the Ostwald ripening and hydrolytic cleavage should be controlled. The diffusion of drug and oil from smaller to larger droplets is referred to as Ostwald ripening which can be arrested by adding 1-3% of an insoluble ripening inhibitor (e.g., squalene or long-chain triglycerides) according to Lifshitz-Slyozov-Wagner (LSW) theory [68]. To avoid chemical degradation, there are two strategies: formulation in buffered aqueous systems at pH 4.8–6.0 (where mupirocin is most chemically stable); incorporation of lipophilic antioxidants (alpha-tocopherol, 0.05–0.1% w/w) to avoid lipid peroxidation [25, 67]. Drug potency of optimized formulations is >98% after 12–24 months of storage [67].

The scale up from laboratory sonication to continuous high-pressure homogenization (HPH; 800–1200 bar, 3–5 cycles) [69] or high-shear rotor-stator systems. During the processing, the temperature should be controlled within 10–15 °C, as the thermal hydrolysis of mupirocin would occur at higher temperatures [69]. The pre-hydrated polymer bases are uniformly nanoemulgated without entrapping air through continuous mixing in the base using the vacuum planetary mixers [38, 69].

7.2 Regulatory Framework for Non-Biological Complex Drugs (NBCDs)

Topical nanoemulsions are considered as Non-Biological Complex Drugs (NBCDs), because the efficacy in clinical use is not only dependent on the identity of the active ingredient but also on the nanostructural architecture [70, 72]. The FDA and EMA have set up regulatory guidelines based on in vitro surrogate tests for non-absorbed topicals: qualitative sameness of excipients (Q1), quantitative sameness within ±5% (Q2), microstructural similarity (droplet size distribution, rheological yield stress, zeta potential) (Q3) [71, 72]. Moreover, *In Vitro* Release Testing (IVRT) through synthetic membranes and *In Vitro* Permeation Testing (IVPT) through dermatomed human skin are valid surrogate tests of bioequivalence and clinical release [71, 72]. Excipients must

be FDA approved for use as Inactive Ingredients (IID) in the FDA Inactive Ingredient Database or be tested in a comprehensive non-clinical study of the safety of the excipient [71].

8. CONCLUSION

Although mupirocin is an important topical antibiotic for treating superficial bacterial infections of the skin, conventional formulations present several drawbacks in terms of the ability of the antibiotic to penetrate the skin, be deposited in the hair follicles, remain stable in the skin, and reach bacteria within biofilm. A nanoemulsion and nanoemulgels based on lipids are promising to overcome these challenges as they can increase the capacity of drug solubilisation, improve the permeation and retention in the cutis, and provide a sustained local drug delivery. Specific inclusion of lipids, surfactants, cosurfactants, and biocompatible gelling agents can also be used to further increase formulation stability, skin residence time, and therapeutic activity. The findings presented in this review suggest improvements in the antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), disintegration of biofilms, and wound healing effects, which are the potential benefits of the preclinical studies. However, the advantages of these should be viewed in the context of the formulations and experimental models tested and for which the clinical significance has not been established.

It is recommended that future research include creating nanoemulsions that respond to environmental changes associated with infection to release mupirocin, and also combining nanoemulsion systems with other sustained release systems, such as biodegradable nanofibers or advanced hydrogel wound dressings. Combination preparations containing the selected bioactive ingredients could also be of interest because of the possibility to combine the antibacterial effect with effective wound healing if the compatibility and safety of the combination is proven. More studies are required to build strong correlation between formulation composition, physicochemical properties, in vitro drug release, in vivo penetration, antimicrobial activity, and safety of the formulation. Systematic quality by design (QbD) practices and suitable comparative testing are also needed to meet long-term stability and batch-to-batch reproducibility, as well as manufacturing scalability and regulatory requirements.

The mupirocin loaded nanoemulsions and nanoemulgels are advanced drug delivery platforms that may be beneficial for topical treatment. Their capacity to overcome well-developed resistance mechanisms and to not develop new resistance and to offer better clinical results needs to be thoroughly validated, however. These formulation would need to be recommended for routine clinical use if they were the result of well-designed clinical trials, extensive safety evaluations, and available and standardized methods of evaluation. With successful translation of the preclinical development to the clinic, mupirocin would have greater therapeutic applications and

could help facilitate development of better delivery systems for topical antimicrobials.

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CONFLICT OF INTEREST: Nil

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