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Various Types of Formulation Used for Treatment of Soft Tissue Infection (STI)

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Abstract: ***Skin and soft tissue infections are usually acute conditions of inflammatory of the skin layers and underlying soft tissues. Skin and soft tissue infection are the most frequent types of infection, generally requiring medical intervention and contribute to morbidity and mortality in both primary care and hospitalised patients. So, the dramatic rise of antibiotic resistance, antiseptic agents can be potential alternatives for the prevention and treatment of SSTIs. In particular, they are commonly recommended in many global practical guidelines for use in per-and postoperative procedures. We are conclude that although nano-technological formulations have demonstrated potential advantages for delivering drugs; nevertheless, there is still scope for traditional formulations and further development of optimised topical formulations to address the rise of antimicrobial resistance.***

Keywords: skin; soft tissue infections; antiseptic; nanocarriers; formulations; nanoparticles

1. Skin and Soft Tissue Infections

The Skin and soft tissue infections refer to acute conditions of inflammatory microbial occupation of the skin layers and soft tissues [1, 2]. In cause have happens on healthcare, not only in middle income countries, but also globally [3]. The Skin and Soft tissues infection is consider as one of the most frequent types of infection, normally require medical intervention and contribute to morbidity and mortality in both primary care and hospitalized patients [2, 4]. In, United States there was an increase of 65% in patients admitted with skin and soft tissue infection in different hospital departments, 32.1 visits per 1000 population in 1997 to 48.1 visits in 2005 [5, 6, 7]. The occurrence of skin and soft tissue infection has increased, possibly as a result of an ageing population, multidrug-resistant strains and the increasing numbers of immune compose patients as a consequence of immune suppressive therapy, cancer, transplant interventions, or HIV/AIDS [2, 8, 9]. The Path physiology of skin and soft tissue infection is related to an interruption in the balance between the immune barrier of the host and the pathogenicity of microbial population colonizing human skin [2]. Interruption of the protective upper layers can be caused by physical and chemical impacts such as ulceration, bites inset, surgical wounds, trauma,, thermal injury or inflammation [2, 10]. Both, patient and the environment are key factors to the risk of developing an SSTI, such as obesity, cardiovascular diseases, critical illness, and chronic kidney disease failure will be at higher risk of skin breakdown, and paralysis that result in the alteration of skin perfusion and temperature control are also considered to be at higher risk, are likely to impair the skin barrier function can be scratching, pressure, shear and friction, UV exposure, or radiation contact in cancer patients [11]. The development of which enables microbes to survive and adapt to un favorable conditions, has become a problem in the healthcare fields, responsible for 65-70% of nosocomial infections [12]. Structure are detachable, affording opportunities for microorganisms to transmit into new sites and spread infections, have been observed in medical devices such as intravenous and urinary catheters, stents, implants. Cell attaching to a surface, multiplying, maturating, and then creating an extracellular polymeric matrix which resists environmental impacts such as mechanical forces and antibiotics [13]. In children, bacterial skin infections are more frequent than fungal, parasitic and viral infections [14]. Gram-positive microorganisms, typically Staphylococcus aureus and beta-hemolytic streptococci [1]. The largest frequent Gram-negative strain isolated was Klebsiella sp. [15]. S. aureus was responsible for more than 40% of total cases in 2003, and was a frequent cause of cellulitis, abscesses and wound infections [2]. The incidence of S. aureus-related skin and soft tissue infections increased two-fold from 2001 to 2009 in the US [16]. It was reported that the proportion of hospital administrations caused by MRSA-related skin and soft tissue infections declined by 29% over the next five years [17]. The Patients with dermatologic conditions often encounter physiological, psychological, as well as financial issues; not only that, many cutaneous concerns can lead to systemic diseases [18]. Moreover, co-morbidity factors, such as diabetes, immune, obesity, liver and kidney failure, and cardiovascular diseases, have repercussions on treatment costs and prolong the length of stay in hospital [19].

2. Antiseptics

Antiseptics are chemicals that people apply to the skin and kill the number of microorganisms living on the skin, in wounds, and in mucous membranes. It is different types of antiseptic vary in cost, effectiveness, uses, and potential side effects. Antiseptic products that can kill or impact the growth of disease-causing bacteria in, or on, living tissue, e. g., on the skin. Antiseptics include rapid bioactivity against bacteria, fungi and viruses, no toxicity or damage to the healthy tissue, and insignificant absorption into the systemic circulation following external application [17]. It is one or more active ingredients and are presented in various

formulations and preparations, for example, antimicrobial hand washes, surgical scrubs, preoperative preparations, tinctures, ointments, creams, mouth-rinses, and toothpaste. They commonly used as pre-operative skin preparations for prevention of surgical site infections [18], as routine skin hygiene such as hand-washes and hand rub products or for treating skin and wound diseases [17]. Skin infections in invasive skin layers, antibiotics are more normally prescribed; in contrast, topical antiseptics are preferred for infections at the outermost surface. The goal is to minimize any microbial colonization in a wound or on the skin surface without causing any deleterious effects on the living tissue or impeding the healing process [17, 19].

2.1 Povidone-Iodine (PVP-I)

Povidone-iodine which is a complex of elemental iodine loosely bound to the carrier polyvinylpyrrolidone, is used as a broad-spectrum antimicrobial agent against bacteria, viruses, fungi, and protozoa at relatively low concentrations [17]. PVP-I is widely used as a topical antiseptic and disinfectant for skin and wound infections, mostly in solution, dry powder and lotion formulations, as an iodophor improves both solubility, stability while releasing the active iodine gradually from the polymer networking over time. So, its residual antimicrobial activity is maintained stably while side effects associated with iodine such as irritation and brown staining on the skin and mucous membranes are reduced. Mechanism of action is unknown, but it is believed that the active iodine species acts as an oxidizing agent which reacts with cell walls, membranes, and cytoplasm by exchanging, functional groups of amino acids (e. g., lysine, histidine, cysteine, and arginine). The consequence is the loss of cell structure and function [17].

2.2 Alcohol

Alcohols are bacteria, fungi, and viruses though less is known about their activity against protozoa and bacterial spores. Isopropyl alcohol, ethanol and n-propanol are the heights alcohols used as antiseptics and disinfectants. Mechanism of action is not clear but they are able to cause precipitation of proteins thus destroying cell membranes. Concentrations from 50% to 80% v/v are recommended for maximum anti-microbial activity because, in more concentrated solutions, alcohol quickly coagulates protein-based molecules present externally on the cell wall and penetration into the cell, so limiting further effects on protein-based inner cell compositions. Stability, and low toxicity, odour and cost. Alcohols are also used as preservatives for biocides such as chlorhexidine [17].

2.3 Triclosan

Triclosan (2, 4, 40-trichloro-20-hydroxydiphenyl ether) is a phenoxyphenol compound it has been considered as an antifungal and antibacterial. [17]. It has a very slow aqueous solubility of 0.012 g/L at 20 °C [19]. It is a common ingredient in various antiseptic products, mainly in antimicrobial body soap, hand washes and toothpaste. It is typically used at concentrations of 0.1 to 2% w/v, on the outside other active antimicrobials such as alcohols, to bring about long-lasting activity on the skin. Triclosan is active and Gram-positive bacteria, including Staphylococcus species. Additionally, it may also have an effect on Gram-negative bacteria and yeast, with some weak activity against enveloped viruses, pseudomonads, and fungi. Triclosan was view to target the cell membrane in a non-specific mechanism, however, recent studies have found a specific bacteriostatic action for triclosan on bacteria through inhibition of the bacterial fatty acid biosynthetic pathway. The higher concentrations found in antiseptic preparations (1–20 mg/mL), there is a hypothesis that triclosan acts as a biocide with multiple actions on lipid, RNA and protein synthesis, leading to cell lysis [20, 21]. Antimicrobial activity of triclosan-containing antiseptics can be affect by formulation effects, for example, there is a synergistic activity with chelating agents (e. g., EDTA) in destroying the Gram-negative bacterial cell wall thereby improving uptake into cells.

3. Topical Antiseptic Formulations

Topical formulatio OR Topical antiseptic formulations. . These were then divided into regular and new antiseptic formulations groups, and their details have been discussed in the following sections.

3.1 Traditional Antiseptic Formulations-

In, this section regularly antiseptic formulations intended for topical delivery will be discussed and a summary of these studies is presented in Table 1.

Table 1: Summarised characteristics of traditional skin antiseptic formulations.

Drug	Concentration	Formulation Type	Combination	Study Characteristics	Carrier Polymer	Manufacturing Technique
Chlorhexidine gluconate (CHG)	-	Dermal polymeric patch		To characterize properties of developed patches regarding their drug release and antimicrobial activity	Eudragit RL100	
Chlorhexidine gluconate	2% CHG in 70% isopropyl alcohol (IPA)	Solution	Acrylate copolymer	To test the effectiveness of adding a film-forming acrylate copolymer to a topical CHG-based preparation on minimizing CHG loss, compared to a marketed CHG solution		
Chlorhexidine gluconate	2% CHG in 70% IPA	Solution		To contrast the residual effects of 2% CHG in 70% IPA v/v and 1% triclosan in 70% IPA v/v on skin bacterial communities		

Isopropanol	75% (w/w)	Hand rub	Glycerol 0.725% (w/w)	To investigate the role of glycerol in pre-surgical hand rub products, based on EN 12791, especially after 3 h of application	-	
Povidone-iodine (PVP-I)	10%	Ointment		To compare the in vitro antibiofilm effect of diluted PVP-I ointment with other six tested products against P. aeruginosa and multi-species biofilms of C. albicans and MRSA		
Triclosan	0.3%	Soap		To study the in vitro and in vivo antibacterial activity in soap		

3.1.1 Solutions

The collation of antiseptic performance of solution formulations is relatively well reported. Specially, in a two-step study, 2% w/v chlorhexidine gluconate in 70% v/v isopropyl alcohol was proven to have extra substantive efficacy against organisms from the skin of human volunteers to 10% w/v sodium hypochlorite and 10% w/v povidone-iodine. Uniformly, it demonstrated a longe-lasting residual effect than triclosan (1% w/v) in 70% v/v IPA, making it more suitable than other antiseptics for procedures similarly, catheter insertion or surgery [22]. Chlorhexidine gluconate 1-2% w/v in 70% v/v ethanol was effective in eradicating multidrug-resistant Acinetobacter baumannii with biofilms with no detected after only 1 min of contact [23]. So, quantitative suspension test to determine the minimal concentrations to achieve at least a reduction of 3.8 log cycles for C. albicans and 4.8 logs for S. aureus and P. aeruginosa, octenidine was more effective than triclosan at all-time points [24]. Nearly, other recent clinical trial found that 70% isopropyl alcohol solution was equivalent to 2% chlorhexidine gluconate in 70% IPA for skin antisepsis [25], the use of cheaper antiseptics like alcohol [24]. Furthermore, it was found that the simultaneous application of 10% w/v PVP-I and a topical antiseptic, Alkosol® (96% ethanol, 30 g isopropanol, and 0.1 g ortophenilphenol), in a two-step pre-operative procedure, reduced the extent of surgical site infections as only 6% o f included patients had at least one symptom of inflammation after 24 h of surgery, compared to 40% for PVP-I alone [25]. Bashir et al. reported that addition of a film-forming polymer such as an acrylate to a pre-operative solution preparation of 2% chlorhexidine in 70% isopropyl alcohol effectively reduced bacterial colonization in an ex vivo model. This was due to the sustained presence of CHG on the skin surface, thus potentially leading to more sustained antimicrobial activity in prevention of surgical site infections [26]

3.1.2 Patch Formulations

A novel mucoadhesive buccal patch which comprised matrix-forming polymers low methoxy amidated pectin (AMP) and 20% w/w Carbopol (CAR) was loaded with 4 mg of triclosan. The patch also included _-cyclodextrin-epichlorohydrin polymer (EPI_CD) and anionic carboxymethylated _-cyclodextrin-epichlorohydrin polymer (CMEPI_CD) to improve triclosan (TCS) solubility, as well as its release from the patch. The TCS-EPI_CD complex did improve solubility, compared to a TCS-parent _-cyclodextrin complex although the presence of 1% (w/v) AMP compromised the complexation and solubilizing properties of both polymeric _-cyclodextrin derivatives (CMEPI_CD and EPI_CD). In addition, the buccal patches formulated with TCS-EPI_CD in combination with AMP-CAR 80: 20 (w/w) provided immediate and stable drug release and efficacy against Streptococcus mutans isolated from the oral cavity [27]. The study evaluate the ability of the polysaccharide psyllium to control the release rate of chlorhexidine from a buccal muco-adhesive patch for local periodontal application. Compound semi-synthetic polymers including sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose (HPMC) with psyllium had the advantages of providing zero-order kinetics for drug release and effective antimicrobial activity against Gram-positive and Gram-negative bacteria [28]. RL 100 complex made up of “ethyl acrylate, methyl methacrylate and slow content of methacrylic acid ester with quaternary ammonium groups” [29]. The amount of quaternary ammonium groups in the RL type is greater than other Eudragit polymers, rendering it more permeable [30, 31]. It is widely used as a drug vehicle, controlled release agent, film former, bioadhesive material or suspending agent [32].

3.1.3 Gels

Gels with creams and ointments, are ordinary semisolid formulations used for dermal applications [33]. Gels may be spread easily a cooling effect as a result of solvent volatilization after application [34]. It can be group into hydrogels and organogels hydrogels mainly include water in the liquid phases, while organogels comprise organic solvents [35]. The term “emugels” (as emulsified gels) is used to biphasic systems which encompass a dispersed aqueous gel and a lipid base. Emugels were developed in order to enhance the occlusive quality of gels [36].

3.1.3 Lotions

Lotions are used particularly (but not popularly in clinical applications) as topical formulations of active substances (i. e., antibiotics, antiseptics, or corticosteroids), intended for treatment of localized cutaneous disorders [34, 35]. Lotions are more easily applied to sizeable skin areas than more viscous creams or ointments [35]. Aqueous antiseptic lotion containing benzethonium chloride (BZT) at 0.2% was reported to have a rapid and wide-spectrum antimicrobial efficacy equivalent to 76% v/v ethanol when was tested according to standard Time-Kill protocols [36]. Combined with its known persistence and low propensity for skin irritation, a BZT-aqueous based antiseptic product has advantages over alcohol-based formulations [37].

3.1.5 Ointments

Ointments are the selected for their tenacity on the skin to extend a drug’s therapeutic activity over a long time as well as producing a protective layer covering the sites of application. They can be associated with irritation due to their occlusive nature arising from their quality [34]. The

combination of ointment, body wash containing tea tree oil at 4% and 5%, respectively, was reported to be better than a ordinary regime consisting of 2% Mupirocin nasal, and triclosan body wash for prevent of MRSA-induced infections. Vitro study tested the PVP-I ointment at numerous concentrations (both standard and diluted concentrations) versus six others antiseptic preparations and a silverbased wound dressing, in terms of eliminating biofilms of Pseudomonas aeruginosa, Candida albicans, and MRSA. Treatment with PVP-I ointment at all concentrations, there was no viable biofilms of P. aeruginosa detected after 4 and 24 h. Also, PVP-I ointment containing 10% w/v active PVP-I was deemed effective at eradiating biofilm materials of C. albicans and MRSA at both 4 and 24 h following application and performed better than the other tested antimicrobial agents [38]

3.1.6 Creams

There are two main types of cream, water in oil and oil in water creams, of which, o/w cream is frequently used to produce a local effect in case of external disorders, skin and wound infections [34]. The therapeutic regime of tea tree oil comprising tea tree oil 5% body wash and tea tree oil 10% cream was proposed for eradicating MRSA colonization. There were no significant changes with the standard therapy of 2% mupirocin nasal ointment, 4% chlorhexidine gluconate soap, and 1% silver sulfadiazine cream [39]

3.2.1 Nanoemulsions

Nanoemulsions are translucent or transparent emulsion systems with droplet sizes less then 500 nm [40]. These colloidal systems can carry effectively both hydrophilic as well as hydrophobic drugs into the skin [40]. As compared to traditional topical preparations like creams, gel and ointments, nanoemulsions have been widely reported to enhance permeation through the skin [41]. A topical o/w nanoemulsion containing cetylpyridinium chloride established activity against a range of pathogenic fungi, including T. mentagrophytes, T. rubrum, E. floccosum, Trichophyton tonsurans, and Microsporum spp. as well as 12 species of hyphaes. Furthermore, it was more active against azole-resistant C. albicans, and azole-susceptible yeast, as compared to other antifungal agents [42]. A benzalkonium chloride loaded nanoemulsion formulation prepared using a high shear homogenization method confirmed efficacious activity against methicillin-resistant Staphylococcus aureus in vitro in mouse and porcine infected wound models. It promoted wound healing as a outcome of reducing inflammation within deep dermal layers and pro-inflammatory cytokine levels [43]. The formulation had formerly been shown to reduce both bacterial colonisation and symptoms of inflammation in the burn wounds [43]. Triclosan based nanoemulsions (NEs) were prepared by high shear homogenization followed by probe ultrasonication and using a range of different concentrations of eucalyptus oil (EO) and olive oil (OO) to dissolve TCS. TCS-loaded NEs containing EO had more benefits over OO and solutions, in terms of both physicochemical properties and skin permeation ability. parallel results were found with nanoemulsions of CHG, as the inclusion of EO improved penetration into the skin, consequently improving drug retention for localized action. Thus, there are opportunities for nanoemulsions for both dermal hydrophobic and hydrophilic drug delivery [44]. A nanoemulsion of tea tree oil prepared using a high speed homogenizer produced wider zones of growth inhibition against all isolated microbes than that available gel products with no observed skin irritation [45]. Tea tree oil were prepared by a low energy method using Tween 80 and Span 80 while Ag NPs were prepared using sodium borohydride as a reducing agent and sodium citrate as a stabilizer. It alloy antibacterial activity against selected microorganisms (from 80 to 95%) at the highest concentration tested (14 _g/mL). More, blending Ag NPs into a nanoemulsion led to synergistic activity against clindamycin-resistant E. coli and an additive influence on S. aureus [46]. Thyme oil nanoemulsion, prepared by an ultrasonication method, were loaded into chitosan–alginate polyelectrolyte complex (PEC) via a casting/solvent evaporation method.

3.2.2 Nanogels

Nanogels are hydrogel globules made up of physically or chemically cross-linked hydrophilic polymer networks [47]. Nanogels are used as dermatological preparations the hypothesis is the entrapment of nanoparticles in the gel matrix will extend exposure times on the skin and as a result, extend the duration of therapeutic potency [48]. Chlorhexidine was incorporated into poly (methyl methacrylate) (PMMA) nanogels with or-cyclodextrin methacrylate (CD-MA). Field-emission-scanning electron microscope (FESEM). This technique was chlorhexidine base (CHX) to be entrapped within the nanogel network and, owing to the presence of CD-MA, CHX was released slow from the material surface into aqueous solution and PBS buffer system due to decomplexation and redispersion of particles. The activity of chlorhexidine base on the growth of S. aureus emerge from not only the nanogel surface, but also the aqueous environment [49].

3.2.3. Nanoparticles

The effects on autotrophic and heterotrophic microbial growth by silver nanoparticles (Ag NPs), silver ions and silver chloride colloids were assessed by Choi et al. (2008). So, to the results of a short-term existent respirometry appraisal, at 1 mg/L silver, silver nanoparticles had a much greater influence on prohibiting nitrifying microbe growth than other forms. Based on an automatic microtiter appraisal, at silver content of 4.2 _M, Ag ions inhibited completely the growth of E. coli. None of three silver forms caused cell membrane lysis at 1 mg/L Ag [50]. Colloidal silver formulations encompassing silver nanoparticles was effective against both Gram-positive and Gram-negative pathogens and excellent fungistatic properties were also reported after 7–14 days contact with the silver colloids, especially in case of systems using poly (N-vinylpyrrolidone) and Na-lauryl sulfate as stabilizers [51]. The antiseptic efficacy of an oil-in-water emulsion containing nanoparticles of polyhexamethylene biguanide hydrochloride (PHMB) was found to be more immediate and long-lasting on human skin colonies in comparison with PHMB solutions, with the duration of effect extending up to 150 min [52].

4. Conclusions

The current review has successfully gathered comprehensive information on various antiseptic formulations employed to prevent and treat skin and soft tissue infections. Its capability to bypass the hepatic first-pass metabolism and easy convenience yet relatively impermeability holds great promise, especially in the treatment of skin infections. This unique advantage allows the application of a wide range of external dosage forms that can be easily removed if necessary. These formulations have evolved from simple ointments, creams, and solutions to advanced nano-technological assisted formulations. However, it is of equal importance that these classy formulations should address clinical and market needs. It is estimated that this review will be a helpful source of formulation scientists to understand and further to develop the antiseptic skin formulations to achieve specific therapeutic objectives.

References

[1] Dryden, M. S. Skin and soft tissue infection: Microbiology and epidemiology. Int. J. Antimicrob. Agents **2009**, 34, 2–7.
[2] Tognetti, L.; Martinelli, C.; Berti, S.; Hercogova, J.; Lotti, T.; Leoncini, F.; Moretti, S. Bacterial skin and soft tissue infections: Review of the epidemiology, microbiology, aetiopathogenesis and treatment. J. Eur. Acad. Dermatol.2**012**, 26, 931–941.
[3] Selcuk, M.; Aysegul, U.; Demet, K.; Kalih, L. C. Bacterial skin infections: Epidemiology and latest research. Turk. J. Fam. Med. Prim. Care **2015**, 9, 65–74.
[4] Vinh, D. C.; Embil, J. M. Rapidly progressive soft tissue infections. Lancet Infect. Dis.2**005**, 5, 501–513.
[5] Hersh, A. L.; Chambers, H. F.; Maselli, J. H.; Gonzales, R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch. Intern. Med.2**008**, 168, 1585–1591.
[6] Lee, G. C.; Boyd, N. K.; Lawson, K. A.; Frei, C. R. Incidence and cost of skin and soft tissue infections in the United States. Value Health **2015**, 18, A245.
[7] Lim, H. W.; Collins, S. A. B.; Resneck, J. S., Jr.; Bolognia, J. L.; Hodge, J. A.; Rohrer, T. A.; Van Beek, M. J.; Margolis, D. J.; Sober, A. J.; Weinstock, M. A.; et al. The burden of skin disease in the United States. J. Am. Acad. Dermatol.2**017**, 76, 958–972.
[8] Esposito, S.; Noviello, S.; Leone, S. Epidemiology and microbiology of skin and soft tissue infections. Curr. Opin. Infect. Dis.2**016**, 29, 109–115.
[9] James, S. L.; Abate, D.; Abate, K. H.; Abay, S. M.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A.; et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases andinjuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet**2018**, 392, 1789–1858.
[10] Moffarah, A. S.; Al Mohajer, M.; Hurwitz, B. L.; Armstrong, D. G. Skin and soft tissue infections. Microbiol. Immunocompromised Host**2016**, 4, 691–708.
[11] Wounds UK. Best Practice Statement: Maintaining Skin Integrity. Available online: https: //www.wound. uk. com/resources/details/maintaining-skin-integrity (accessed on 19 December 2019).
[12] Malheiro, J.; Simões, M. Antimicrobial resistance of biofilms in medical devices. In Biofilms and Implantable Medical Devices; Deng, Y., Lv, W., Eds.; Woodhead Publishing: Cambridge, UK, 2017; Chapter 4; pp.97–113.
[13] English, J. S. C. General Dermatology: An Atlas of Diagnosis and Management; Clinical Publishing: Oxford, UK, 2007.
[14] World Health Organization. Epidemiology and Management of Common Skin Diseases in Children in Developing Countries. Available online: https: //apps. who. int/iris/handle/10665/69229 (accessed on 15 December 2019).
[15] Poulakou, G.; Lagou, S.; Tsiodras, S. What's new in the epidemiology of skin and soft tissue infections in 2018? Curr. Opin. Infect. Dis.2**019**, 32, 77–86.
[16] Berríos-Torres, S. I.; Umscheid, C. A.; Bratzler, D. W.; Leas, B.; Stone, E. C.; Kelz, R. R.; Reinke, C. E.; Morgan, S.; Solomkin, J. S.; Mazuski, J. E.; et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. JAMA Surgery **2017**, 152, 784–791.
[17] Claesen, J. Topical antiseptics and the skin microbiota. J. Investig. Dermatol.2**018**, 138, 2106 2107.
[18] Williamson, D. A.; Carter, G. P.; Howden, B. P. Current and emerging topical antibacterials and antiseptics: Agents, action, and resistance patterns. Clin. Microbiol. Rev.2**017**, 30, 827–860.
[19] Lee, J.; Kwack, S.; Shin, C.; Jang, H.-J.; Kim, H.; Kim, M.; Seo, D.-W.; Lee, B.; Kim, K.-B. Risk assessment of triclosan, a cosmetic preservative. Toxicol. Res.2**019**, 35, 137–154.
[20] Schweizer, H. P. Triclosan: A widely used biocide and its link to antibiotics. FEMS Microbiol. Lett.2**001**, 202, 1–7.
[21] Bashir, M. H.; Hollingsworth, A.; Schwab, D.; Prinsen, K. S.; Paulson, J. E.; Morse, D. J.; Bernatchez, S. F. Ex vivo and in vivo evaluation of residual chlorhexidine gluconate on skin following repetitive exposure to saline and wiping with 2% chlorhexidine gluconate/70% isopropyl alcohol pre-operative skin preparations. J. Hosp. Infect.2**019**, 102, 256–261.
[22] Chiang, S.-R.; Jung, F.; Tang, H.-J.; Chen, C.-C.; Chen, C.-H.; Chou, H.-Y.; Chuang, Y.-C. Desiccation and ethanol resistances of multidrug resistant Acinetobacter baumannii embedded in biofilm: The favorable antiseptic efficacy of combination chlorhexidine gluconate and ethanol. J. Microbiol. Immunol. Infect.2**018**, 51, 770–777.
[23] Martínez, J. M. D.; Macías, J. H. M. D.; Arreguín, V. M. D.; Álvarez, J. A. M. D.; Macías, A. E. M. D.; Mosqueda-Gómez, J. L. M. D. Isopropyl alcohol is as efficient as chlorhexidine to prevent contamination of blood cultures. Am. J. Infect. Control.2**017**, 45, 350–353.
[24] Djozic, H.; Pandza, H.; Hasukic, S.; Custovic, S.; Pandza, B.; Krupalija, A.; Beciragic, E. Efficiency of

local antiseptic alkosol (ethanol, isopropanol-30 g and ortophenilphenol) and povidone iodide on the incidence of surgical site infection after inguinal hernioplasty. Med. Arch.2**016**, 70, 108–111.

[25] Caelli, M.; Porteous, J.; Carson, C. F.; Heller, R.; Riley, T. V. Tea tree oil as an alternative topical decolonization agent for methicillinresistant Staphylococcus aureus. J. Hosp. Infect.2**000**, 46, 236 237.

[26] Picheansathian, W. A systematic review on the effectiveness of alcohol-based solutions for hand hygiene. Int. J. Nurs. Pract.2**004**, 10, 3–9.

[27] Koburger, T.; Hübner, N.-O.; Braun, M.; Siebert, J.; Kramer, A. Standardized comparison of antiseptic efficacy of triclosan, PVP–iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. J. Antimicrob. Chemother.2**010**, 65, 1712–1719.

[28] Sonje, A.; Chandra, A. Comprehencive review on eudragit polymers. Int. Res. J. Pharm.2**013**, 4, 71–74.

[29] Kaur, G.; Grewal, J.; Jyoti, K.; Jain, U. K.; Chandra, R.; Madan, J. Oral controlled and sustained drug delivery systems: Concepts, advances, preclinical, and clinical status. In Drug Targeting and Stimuli Sensitive Drug Delivery Systems; Grumezescu, A. M., Ed.; William Andrew Publishing: Boston, MA, USA, 2018; Chapter 15; pp.567–626.

[30] Brady, J.; Dürig, T.; Lee, P. I.; Li, J. X. Polymer Properties and Characterization. In Developing Solid Oral Dosage Forms; Qiu, Y., Chen, Y., Zhang, G. G. Z., Yu, L., Mantri, R. V., Eds.; Academic Press: Boston, MA, USA, 2017; Chapter 7; pp.181–223.

[31] Patra, C. N.; Priya, R.; Swain, S.; Kumar Jena, G.; Panigrahi, K. C.; Ghose, D. Pharmaceutical significance of Eudragit: A review. Future J. Pharm. Sci.2**017**, 3, 33–45.

[32] Benson, H. A. E.; Watkinson, A. C. Topical and Transdermal Drug Delivery: Principles and Practice, 1st ed.; Wiley: Hoboken, NJ, USA, 2011.

[33] Jones, D. S. Pharmaceutics: Dosage Form and Design; Pharmaceutical Press: London, UK, 2016.

[34] Mahato, R. I.; Narang, A. S. Pharmaceutical Dosage Forms and Drug Delivery, 2nd ed.; CRC Press: Boca Raton, FL, USA, 2012.

[35] FDA-Tentative Final Monograph. Topical antimicrobial products for over-the-counter-use, 21 CFR 333 and 369. Fred. Regist.1**994**, 59.

[36] Erasmus, V.; Daha, T. J.; Brug, H.; Richardus, J. H.; Behrendt, M. D.; Vos, M. C.; van Beeck, E. F. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect. Control. Hosp. Epidemiol.2**010**, 31, 283–294.

[37] Liang, X.-J. Nanopharmaceutics: The Potential Application of Nanomaterials; World Scientific: Hackensack, NJ, USA, 2013.

[38] Cao, Z.; Spilker, T.; Fan, Y.; Kalikin, L. M.; Ciotti, S.; LiPuma, J. J.; Makidon, P. E.; Wilkinson, J. E.; Baker, J. R., Jr.; Wang, S. H.

[39] Nanoemulsion is an effective antimicrobial for methicillin-resistant Staphylococcus aureus in infected wounds. Nanomedicine **2017**, 12, 1177–1185.

[40] Pannu, J.; McCarthy, A.; Martin, A.; Hamouda, T.; Ciotti, S.; Fothergill, A.; Sutcliffe, J. NB-002, a Novel Nanoemulsion with Broad Antifungal Activity against Dermatophytes, Other Filamentous Fungi, and Candida albicans. Antimicrob. Agents Chemother.2**009**, 53, 3273–3279.

[41] Ulmer, M.; Patzelt, A.; Vergou, T.; Richter, H.; Müller, G.; Kramer, A.; Sterry, W.; Czaika, V.; Lademann, J. In vivo investigation of the efficiency of a nanoparticle-emulsion containing polihexanide on the human skin. Eur. J. Pharm. Biopharm.2**013**, 84, 325–329.

[42] Kakadia, P. G. Formulation and Evaluation of Nanoencapsulated Antimicrobial Agents for Dermal Delivery. Ph. D. Thesis, University of Huddersfield, Huddersfield, UK, 2016.

[43] Sinha, P.; Srivastava, S.; Mishra, N.; Singh, D. K.; Luqman, S.; Chanda, D.; Yadav, N. P. Development, optimization, and characterization of a novel tea tree oil nanogel using response surface methodology. Drug Dev. Ind. Pharm.2**016**, 42, 1434–1445.

[44] Najafi-taher, R.; Ghaemi, B.; Kharazi, S.; Rasoulikoohi, S.; Amani, A. Promising antibacterial effects of silver nanoparticle-loaded tea tree oil nanoemulsion: A synergistic combination against resistance threat. AAPS PharmSciTech.2**018**, 19, 1133–1140.

[45] Cao, Z.; Spilker, T.; Fan, Y.; Kalikin, L. M.; Ciotti, S.; LiPuma, J. J.; Makidon, P. E.; Wilkinson, J. E.; Baker, J. R., Jr.; Wang, S. H. Nanoemulsion is an effective antimicrobial for methicillin-resistant Staphylococcus aureus in infected wounds. Nanomedicine **2017**, 12, 1177–1185.

[46] Ulmer, M.; Patzelt, A.; Vergou, T.; Richter, H.; Müller, G.; Kramer, A.; Sterry, W.; Czaika, V.; Lademann, J. In vivo investigation of the efficiency of a nanoparticle-emulsion containing polihexanide on the human skin. Eur. J. Pharm. Biopharm.2**013**, 84, 325–329.

[47] Hemmila, M. R.; Mattar, A.; Taddonio, M. A.; Arbabi, S.; Hamouda, T.; Ward, P. A.; Wang, S. C.; Baker, J. R., Jr. Topical nanoemulsion therapy reduces bacterial wound infection and inflammation after burn injury. Surgery **2010**, 148, 499–509.

[48] Zhang, H.; Zhai, Y.; Wang, J.; Zhai, G. New progress and prospects: The application of nanogel in drug delivery. Mater. Sci. Eng. C.2**015**, 60.

[49] Petica, A.; Gavriliu, S.; Lungu, M.; Buruntea, N.; Panzaru, C. Colloidal silver solutions with antimicrobial properties. Mater. Sci. Eng. B **2008**, 152, 22–27.