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Review Article

Topical Antimicrobial Microparticle-Based Polymeric Materials for Burn Wound Infection

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ABSTRACT

Microparticles are one of the delivery systems which protect drugs from the harsh environments and also can stabilize drugs or eliminate discrepancies. The aim of this study was to discuss topical microparticle delivery system which contains natural oils for burn wounds and also to classify burns and wound healing process. This scoping review consists of 50 publications from periods between 2016 and 2020 which resulted from the extraction of 63 publications from search engines using various keywords. Data of publications that met the inclusion and exclusion criteria were extracted manually. Most publications presented on burn wound treatment used microparticles containing synthetic drugs and natural oils. The review also pointed at a wide variety of topical product dosage forms related to formulations that range in consistency from liquid to semi-solid preparations, but the most popular product is the semi-solid preparations. The use of natural oils in topical microparticles using natural or synthetic polymers provides more advantages and is recommended for drug or cosmetic development specifically in wound care.

Keywords: Burn, Bacterial infection, Human skin, Microparticles, Topical, Wound.

Introduction

Microparticles are particles with a size range of 1–1000 µm.[1] They are employed in the delivery systems as a drug carrier. Microencapsulation is a technique used to protect the drugs from exposure to a harsh environment, stabilize drugs, eliminate discrepancies, or mask unpleasant tastes. A drug-delivery system using microparticles aims at maximizing drug bioavailability while minimizing side effects.[2] Microparticles are a type of drug delivery system that is characterized by their small size and high carrier efficiency. This delivery system offers many advantages including increasing efficacy, reducing toxicity, and increasing patient compliance.[3] Drug release from microparticles has several mechanisms such as delayed, sustained, or controlled release. The release of a drug is also affected by polymers including natural or synthetic polymers. Mechanisms, physicochemical properties, and activities are all influenced by polymers. Some of the polymers used in microparticles have been applied for wound healing purposes.[4]
The aim of this scoping review was to survey the literature to determine the uses of topical antimicrobial microparticles of polymeric materials in the treatment of burn wound infection.

Materials and Methods

This scoping review consists of 50 publications from the periods between 2016 and 2020. Sixty-three publications were extracted from a search engine using various keywords. Burn wounds, wound healing, bacterial infection, microparticles based on polymeric materials, and topical formulation were some of the terms used. Data of publications that met the inclusion and exclusion criteria were extracted manually. The inclusion criteria were publications that contain: topical microparticles delivery systems for burn healing; classification of burns and the wound healing process; natural oils that have antimicrobial effects and various polymers which are commonly used in burns. The exclusion criteria were articles in languages other than English and publications which did not describe parameters of the physicochemical properties of the delivery system.
Data extraction was then explained more by a description of common microbial species that caused wound healing and examples of currently available antimicrobial drugs; explanation of natural oils that have antibacterial activity as well as antimicrobial agents that are commonly used in wound care; topical microparticles and polymers which are commonly used in burns and information of uses of drug delivery in various animal models.

Results and Discussion

Burn category and therapy
Burn is defined as a traumatic injury resulting from coagulative destruction of the skin that can be caused by touching the body surface with chemicals, electricity, radiation, or objects that produce heat, either by direct or indirect contact.[5] Severe burn causes chronic wounds, skin contractures, loss of body fluids, and wound infections.[5,6] Individual burn injuries vary greatly depending on burn depth, surface area, heredity, immunological competence, and age. Furthermore, another extrinsic complication leads to prolonged inflammation and delays epithelialization.[6] Burn can be categorized into three groups, such as first-, second-, and third-degree burn.[7,8,9] Its classification based on three degrees of severity is illustrated in Fig 1. First-, second-, and third-degree burns are categorized and characterized based on the depth of the injury. This results in hair follicle damage and skin color changes. Some wounds heal with scarring and contractures for longer time.[10] Second-degree burns can result from contact with liquids or hot surfaces. If left untreated, it can become a third-degree burn with increased edema formation.[11] Second-degree burn requires conservative treatment with topical materials and wound dressings. In third-degree burns, the entire dermis and all deep epidermal parts are destroyed.[5]

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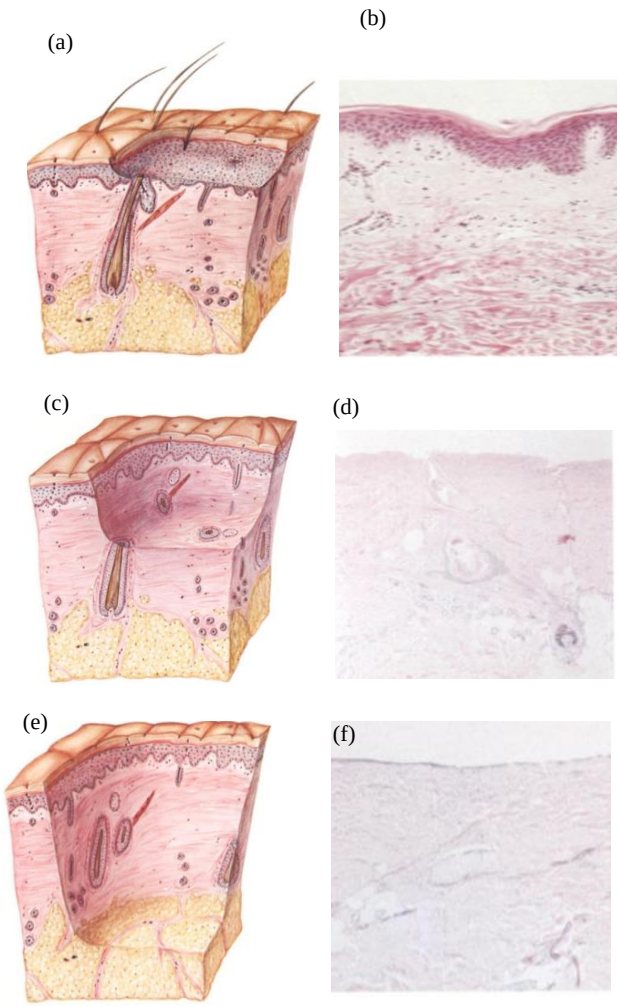

Figure 1: Burn wound categorization according to depth. A: First-degree burn; b: Histological section of first-degree burn; c: Second-degree burn; d: Histological section of second-degree burn; e: Third-degree burn; f: Histological section of third-degree burn.[5]

Topical materials commonly used for pharmacological therapy in second-degree burns are summarized in Table 1.

Wound healing process

The skin is the largest organ in the human body and responsible for a protective barrier at the interface against pathogens and microorganisms. It is directly exposed to harmful microbial, mechanical, chemical, and thermal agents.[12] Burns and chronic long-term wounds are the most common causes of skin damage.[13] Figure 2 gives an illustration of skin structure and degree of burns.

Synchronization of different cells is required for skin repair. The epidermis contains sebaceous and sweat glands, as well as hair follicles. The dermis is rich in extracellular matrix (ECM), blood vessels, and sensor receptors to provide strength, nutrition, and immunity to the skin. The source of growth factors to the dermis is subcutaneous adipose tissue. When skin is injured, some cells need to be coordinated.[14,15] The normal wound healing phase is shown in Figures 3 and 4. Biochemical and cellular signals will initiate wound healing process when skin integrity is compromised, either through injury or disease. Hemostasis describes the initial and cellular phases which includes inflammation, proliferation, and remodeling.[6]

Wound healing phases

Wound healing phases are divided into inflammatory, proliferative, and remodeling.[18] Infection is the most common cause of burn complications. It is associated with microbial development, as well as decreased resistance to skin mechanical integrity and general immunological suppression. Eschar restricts the dispersion of antibiotics given systemically due to their avascularity.[19] Figure 5 shows an open wound that is prone to bacterial contamination and the effect of administering an antimicrobial agent. The antimicrobial agent acts as a physical barrier to prevent pathogens from entering the wound or to kill invading microorganisms to support the healing process by stimulating the immune system and fibroblast/keratinocyte migration.[20]

Chronic wounds usually contain *Staphylococcus aureus* (63%) and *Pseudomonas aeruginosa* (25%).[21,22] Bacteria will directly compete for nutrients from host tissue, and bacterial growth will be aided by a protein.[23] Ability to manage wound infection, generate a moist environment, protect wound area, stop bleeding, absorb exudate, improve wound healing, ease of use, sterilization, biodegradability, and non-toxicity are important elements to consider when choosing burn-suitable material. Various topical formulations such as ointments and creams have been used for wound protection.[24]

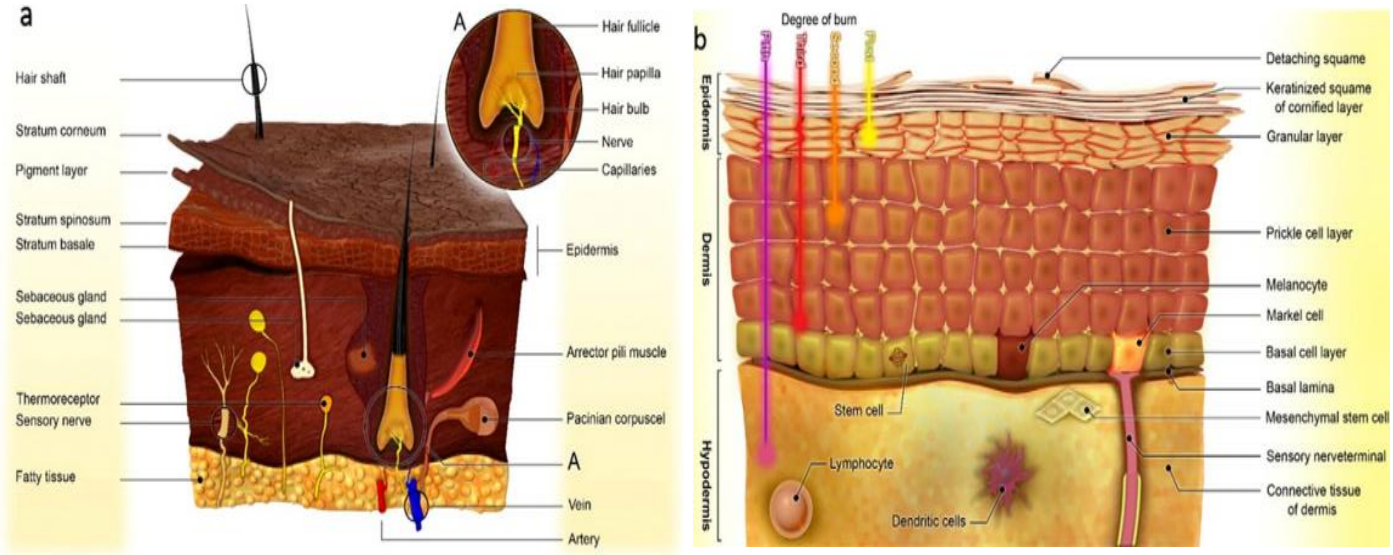

Figure 2: Schematic illustration of (a) skin structure; and (b) degree of burns including epidermis, dermis and hypodermis layers, as well as constituent cells and their sub-layers.[15]

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Table 1: Commonly used topical substances used for pharmacological therapy in second-degree burn[6]

Class	Agent	Route of administration	Commercial product of burns and/or scars
Anti-inflammatory therapies	Corticosteroids	Topical, intralesional	Yes (off-label)
	Calcineurin inhibitors	Topical, intradermal	Some (off-label)
	F-5 fragment of heat shock protein-90a	Topical	No (under investigation)
Antimicrobial therapies	Gentamicin	Topical	Yes
	Neomycin	Topical	Yes
	Metronidazole	Topical	Yes (off-label)
	Silver	Topical	Yes
	Honey	Topical	Yes
	Povidone iodine	Topical	Yes
	Cadexomer iodine	Topical	Yes
Antifibrotic therapies	Nintedanib	Undetermined	No
	Pirfenidone	Topical	No
	Retinoids	Topical	Yes (off-label)
Beta-blockers	Propranolol	IV	Yes (off-label)
	Timolol	Topical	Yes (off-label)
Growth factors	Becaplermin	Topical	Yes (off-label; FDA approved)
	Basic fibroblast growth factor	Topical	Yes (not FDA-approved but may be found in topical cosmeceuticals)

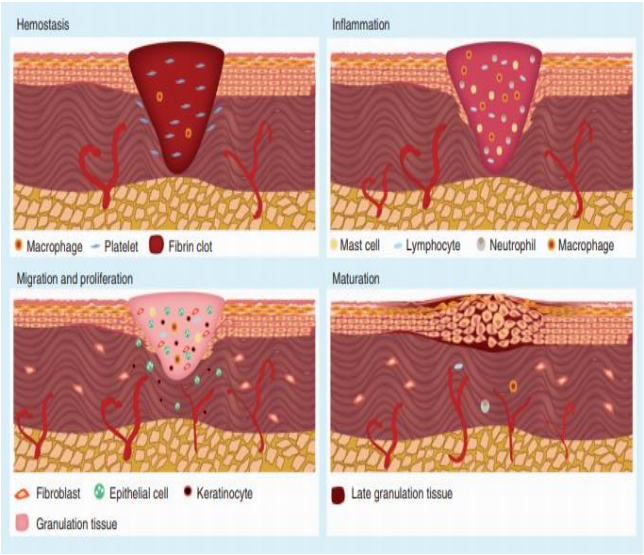

Figure 3: Wound healing process.[16,17]

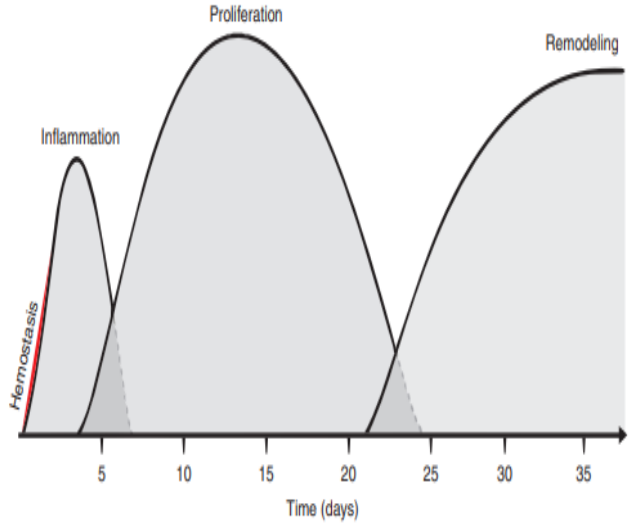

Figure 4: Graphical depiction of wound healing phases and their timeline.[6]

Types of microbes and antimicrobial agents that support the wound healing process are presented in Table 2. Also, antimicrobial agents used in wound care are shown in Table 3. Topical application of controlled-release antimicrobials to chronic wounds is more beneficial than systemic application.[26]

Since chronic wound surfaces often lack adequate blood supply, substantial dosages of antibiotics are required to control infection. Drug encapsulation for long-term release has the potential to improve drug safety. Controlled drug delivery systems such as microparticles, solid lipid nanoparticles (SLN), and liposomes have been formulated for better healing.[27]

Topical medicinal application

Topical medicines are applied for promoting the healing process and preventing infection of all wound types. This minimizes free radicals, which is beneficial for wound formulations.[25] Nano-DDS has great potential in increasing the efficacy of drug therapy due to its ability to avoid degradation and maintain release. Skin regeneration and wound healing are improved by DDS.[25,28] Table 4 depicts the characteristics and advantages of the DDS formulation.

Nanoparticle drug delivery system in burn treatment

A new method has been developed to produce a hybrid gel membrane containing AgNP.

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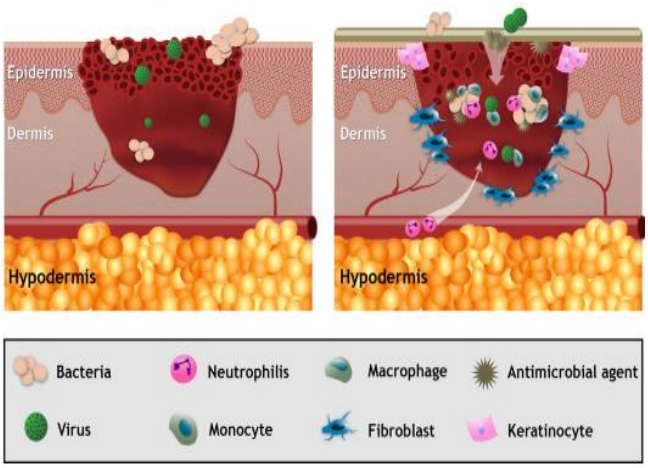

Figure 5: Wound management. a: The process of healing in an open wound; b: Closing the wound by administering antimicrobial agents.[20]

Antibacterial activity of the AgNP-BC membrane was studied against gram-negative and positive bacteria. The results indicated that the composite membrane filled with AgNP inhibited the growth of all bacteria. No inhibitory effect was observed for pure BC membrane (control), thus indicating an important role for AgNP in providing resulting antimicrobial properties.[29] Microspheres and nanospheres are colloidal systems using natural or synthetic materials, such as alginate, chitosan, gelatin, or PLGA. This type of polymer is widely used for DDS for wound therapy.[25,30] Hydrogel is designed to hold moisture on the wound surface for healing and maintain skin hydration. It is made from different polymers and has been used extensively for wound care. This hydrogel is a very attractive DDS because it is easy to prepare and allows continuous drug administration. Drug release rate depends on the size in the tissue and the release can be modulated by increasing or decreasing the degree of polymer cross-linking or swelling.[31] Liposomes are a type of carrier with a hydrogel core that improves cell stability and promotes cell proliferation.[32] Wounds are effectively covered by liposome.[33]

Table 2: Microbial species and antimicrobial drugs for wound healing[6]

Category	Species	Antimicrobial agents				
		Silver nitrate (AgNO3)	**Silver sulfadiazine**	**Mafenide acetate**	**Nanocrystalline silver dressings**	**Bacitracin zinc**
Gram-positive	*Staphylococcus aureus* Methicillin-resistant *S. aureus* (MRSA) Coagulase-negative Staphylococci	-	-	-	Active against aerobic gram-negative bacilli, aerobic gram-positive bacilli, MRSA, and VRE Some eschar penetration and Limited toxicity	Narrow spectrum against gram-positive cocci, especially *Staphylococci* and beta-hemolytic *Streptococci* No eschar penetration and Minor dermatological irritant
	Enterococcus spp. Vancomycin-resistant enterococci (VRE)	-	-	Bacteriostatic against aerobic	-	-
Gram-negative	*Pseudomonas aeruginosa* *Escherichia coli* *Klebsiella pneumoniae* *Serratia marcescens* *Enterobacter* spp. *Proteus* spp. *Acinetobacter* spp. *Bacteroides* spp.	Bacteriostatic against aerobic gram-negative bacilli No eschar Penetration and Electrolyte imbalance	Bactericidal against aerobic gram-negative bacilli No eschar Penetration and Leukopenia	gram-negative bacilli and anaerobes Eschar Penetration, Painful and Metabolic acidosis	-	-

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Table 3: Antimicrobial agents used for wound care[25]

Antimicrobial agents	Administration	Bacteria
Tetracycline	Oral/Topical	Gram-positive and negative
Neomycin	Systemic/Topical	Aerobic Gram-negative bacilli and Gram-positive
Mupirocin	Topical	Gram-positive bacteria especially MRSA, some Gram-negative flora
Amphotericin B	Systemic/Topical	Fungi
Silver sulfadiazine	Topical	Gram-positive, most Gram-negative bacteria, and some fungal forms
Mafenide acetate	Topical	Gram-negative bacilli, anaerobes

Table 4: Types and characteristics of DDS[26]

Drug Delivery System	Characteristics	Advantages
Polymeric nanoparticles	Very small size (1-1000 nm)	Increase drug solubility and stability, maintain antimicrobial, sustain release.
Microspheres	Small size (1-1000 μm) Biocompatible	High encapsulation, increase occlusive, enhance stability.
Hydrogels	Biocompatible and biodegradable	Prevent wound dehydration, high drug loading.
Liposomes	Vesicular structures resemble lipid cell membrane of the body	High encapsulation, improve permeability and stability.
Solid Lipid Nanoparticles	Biocompatible and degradable lipids	Suitable for damaged or inflamed skin, sustain release, high encapsulation efficiency.
Nanofiber mats	High surface to volume ratio and highly porous	Promote cell respiration and skin regeneration, sustain release, good mechanical properties.
Wafers and Sponges	Lyophillised Extremely porous structures	Easy to applyhigh drug loading, sustain release, enhance drug stability.

Nanofibers are three-dimensional (3D) networks capable of mimicking natural ECM, which is necessary for the interconnection of cells and dissolved factors, as well as the complete regeneration of injured tissue and biological function. They can also be made by using a combination of two or more polymers.[34] Combination of polymers, poly ε-caprolactone, and PEG to entrap GF126 has been studied and showed the effectiveness of electrospun rhEGFs in diabetic mouse model.[35]

Microparticle polymer and burn healing process

Polymer remains the most versatile biomaterials which has been used in medicine, biotechnology, and cosmetic industries. The use of various polymers to encapsulate drugs results in an optimum pharmacokinetic profile. Localized drug delivery, continuous drug delivery, drug stabilization, lower release rates, and more steady release rates are the main benefits.[3] The types of polymers commonly used in burns and their outcomes are summarized in Tables 5 and 6. When a gelling component is added to a microemulsion, it forms a hydrogel, which creates more stable formulas than liquid formulations. Hydrogels based on stable microemulsions have strong permeability and a viscosity suitable for topical application, providing longer-term skin contact.[36]

In Vivo Animal Models

Burn healing process can be studied by *in vitro* and *in vivo* tests using animal models. Animal trials are used to investigate wound healing problems, as well as to assess burn pathology, the effects of drugs or biomaterials on burns, the consequences of burn trauma, and the development of new therapeutic agents. Availability, cost, easy to use, and anatomical similarities to humans affected selection of animal burn models.[40] Comparison of human skin with animal skin models is presented in Table 7. Wound healing studies have included small animals such as mice, rats, and rabbits, as well as larger animal models such as pigs. Mice are not clinically relevant due to their higher resistance to infection. Wound contracture is more important than scar tissue formation in wound healing. Rats are aggressive animals that are difficult to handle. Human skin has less elasticity, as such rabbits are a better choice.[41] Infection can be induced in animal models by *P. aeruginosa* and *S. aureus*. The burn application model can be seen in Table 8. Researchers have looked into the possibilities of natural oils as burn wound agents,[11,42,43] as shown in Table 9. The microencapsulation technique for microparticle formation of natural oils is summarized in Table 10.

Characteristics of microparticles

The characteristics of microparticles are observed from the angle of particle size and surface morphology. Particle size is important to study the physical characteristics of microparticles. Different techniques used for size measurement include microscopy (optical or electron), sieving, sedimentation, or automatic such as particle counter, light scattering, flow cytometry, and field flow fractionation.[3] Concerning surface morphology, scanning electron microscopy (SEM) can reveal the porosity and microstructure of the drug delivery system.[3]

Studies on microparticles concerning burn

The behavior of DDS in terms of drug release and its efficacy can be observed by *in vitro* release tests. Drug release from the polymer occurs by diffusion in an *in vitro* environment and is determined by polymer degradation.[3] However, *in vivo* study is a key component of any study because it provides efficacy of microparticles for understanding the characteristics of formulations in biological systems.[3] *In vivo* study includes tissue histology analysis, *in vivo* penetration, and activity testing. The histological analysis of burn infection is performed to observe microorganisms invading the living tissue below the surface of the eschar. The main advantage of histological analysis is to understand burn degree level and depth.[23, 46, 47] Another analysis conducted in burn analysis is related to the bioadhesivity. This test is performed to determine how long the preparation is in contact with the skin. The longer the contact time is, the more drug has penetrated the skin.[48]

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Table 5: Polymers commonly used in burn treatment[3]

Polymers	Materials
Non-Biodegradable Polymers	Polyethyl urethane (PEU), Ethyl cellulose, PVA, PVC, polydimethyl siloxam, Cellulose acetate.
Hydrogels	Crosslinked polyvinyl alcohol (PVA), PEMA, PVP, Polyacrylamide, Dextran.
Dissolved Polymers	PEG, APMC, methacrylic acid copolymers, and Eudragit L.
Biodegradable Polymers	PLA, PGA, PCL, PLGA.

Table 6: Polymers commonly used in topical microparticles for burn preparations

Polymers	Drugs	Route of administrations	Outcomes	References
Chitosan	Chamomile	Topical	Chitosan coated shows skin hydration	37
Sodium alginate (SA) and kappacarrageenan (k-Ca)	Silver nitrate	Topical	Increases absorption of exudate thereby promoting effective proliferation, dense fibrous facilitates healing of second-degree burn.	38
phosphatidylcholine	LL37	Topical	Increases antibacterial activity against S. aureus and E. coli. Decrease inflammatory cytokines	39
Collagen-chitosan	silver sulfadiazine	Topical	Accelerates skin regeneration, resistant to Gram-negative and Gram-positive bacteria	40

Table 7: Comparing human skin with various animal models.[41]

Animal models	Advantages	Disadvantages
Pig	Anatomical and physiological similarities with human. Fewer variations.	Not affordable. Difficult to handle, store, and obtain. Higher growth rates and excess body weight
Rat	Small size, easy to obtain and maintain. Quick reproduction	Unlike humans in terms of size, anatomy, and metabolic features
Rabbit	Similar in kinetics and patterns of post-thermal injury change. Cost effective.	High risk of infection and more expensive than rat
White rat	Easy to obtain and maintain, cheap, lower mortality, reduced treatment time, superior immune system	An important difference in the healing stage. Dense hair on the skin of rat.

Table 8: Classification of burn induction in experimental animals.[15]

Classifications	Applications
Gas flame burn model	
Katakura burn model	Using a frame equipped with window placed on the shaved rat's back, followed by heating to produce third degree burn.
Burning ethanol bath burn model	
Stieritz-Holder burn model	Rat is anesthetized and shaved followed by filling asbestos with windows and allowed to burn.
Pre-heated single metal plate/bar burn models	
Tavares burn model	Heating with aluminum rod and pressed against the shaved back.
Orenstein burn model	Heating with preheated plate at 150°C then pressed against the guinea pig.
Boiling or hot water burn models	
Suzuki burn models	Male Wistar rat skin touched with a glass chamber device over a period of seven days.

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Bahar burn model	Absorbent cloth was soaked in boiling water and rubbed on the back of rat with varying times.
Bjornson burn model	Immersed area of female or male guinea pig at 99°C for 13 seconds.
Mason and Walker burn model	Hole size is determined. Animal is sedated, shaved on the back, and followed by supine placement on the template. The exposed area is immersed produce model burns with partial thickness (as second degree) and full thickness (as third degree).
Kaufman burn model	Cylindrical aluminum rod was heated to create partial deep skin thickness on the back of anesthetized rabbit.
Stevens burn model	Brass blocks are preheated side of the back mouse skin.

Table 9: Natural oils for the treatment of second-degree burn wound

Oils	Chemical compounds	Therapeutic action	References
Argan oil	Tocopherol	Antioxidant, anticancer, antithrombotic, and antihypertensive effects	11
Olive oil	Mineral, vitamin, and unsaturated oil	Antioxidant and antimicrobial	44
Crocodile oil	Saturated and unsaturated fatty acids	Antinociceptive and anti-inflammatory	45
Lavandula angustifolia	Linalool, linalyl acetate, lavandulol, lavandulyl acetate, camphora	Analgesia, antibacterial, antifungal, antidepressant, antispasmodic, balancing, and sedation	46
Wild orange	Monoterpenes, tetraterpenes, aldehydes, alcohols, ketonesa	Antiseptic, antimicrobial, antiplasmid	45
Cinnamon	Aldehydes, phenols, alcohols, sesquiterpenes, carboxylic acid	Astringent, germicide, antibacterial, antifungal, antimicrobial	45
Clove oil	Oxides, monoterpenes, alcohols, aldehydesd	Anesthetic, antiseptic	45

Table 10: The techniques used in microencapsulation of natural oils.[3]

Microencapsulation methods	Materials Investigated Shell (core)	Applications
Chemical methods		
Emulsion polymerization	Poly(acrylate)s [Insulin]	Drug delivery
Dispersion	Poly (2-hydroxyethyl-co-glycidyl methacrylate) [ferrofluid], Poly(N-vinylα-phenylalanine) [fluorescein isothiocyanate]	Biosciences
Interfacial	Polyurea [insecticides, catalys], Polyamide [oils], Polyurethane [insecticides], Polyester [protein]	Crop protection, Catalysis, Drug delivery
Physical/Mechanical methods		
Suspension crosslinking	Protein, Albumin [doxorubicin, magnetite], polysaccharides	Drug delivery
Solvent evaporation/extraction	Poly(lactide), {oly(lactide-co-glycolide) [drugs]	Drug delivery
Coacervation/Phase separation	PGLA [Triptorelin], PLGA [Octreotide]	Drug delivery
Spray drying	PGLA [Bromocriptine]	Drug delivery
Precipitation	Phenolic polymers [enzymes]	Biocatalysis
Co-extrusion	Polyacrylonitrile [hepatocytes]	Biomedical
Layer by layer deposition	Polyelectrolytes [organic compounds]	Biosensor
Supercritical fluid expansion	Poly(ethylene glycol) [felodipine]	Drug delivery
Impregnation	Amberlite [Benzoic acid]	Drug delivery

Antibacterial activity testing
To demonstrate potential as an antibacterial agent, *in vitro*, and *in vivo testing* can be carried out. In the *in vitro* activity test, antibacterial

efficacy is assessed by observing the inhibition zone diameter. Also, the determination of minimal inhibitory concentration (MIC) is a key indicator of the potency of an antibacterial agent.[49]

In vivo activity test with fibroblast core area measurement
The area of the fibroblast core is measured to estimate wound closing activity. Fibroblasts infiltrate and degrade fibrin clots.
The complex matrix supports and regulates fibroblast migration, activity and act as a support and signal for angiogenesis, granulation tissue formation, and epithelialization.[50]

Conclusion

The advantages of topical microparticles for skin diseases such as a burn or wound therapy have been widely explored. Topical materials commonly used for pharmacological therapy in second-degree burns are synthetic antimicrobial agents and natural oils. Microparticles as one of the drug delivery systems could be an alternative to antimicrobial in second-degree burn wound infection.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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