Development of Hydrogel-Based Sprayable Wound Dressings for Second- and Third-Degree Burns

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1. Development of Wound Dressings for Burns

1.1. Skin Physiology

Skin is the largest organ in the human body. It is composed of two layers: a superficial layer called the epidermis and a deeper layer called the dermis. The cells within the epidermis replicate and differentiate in the basal layers before being pushed toward the uppermost epidermal layer. The upper epidermal layer, known as the horny layer, functions as a semipermeable barrier, prevents water and salt loss, and blocks the entry of foreign matter (e.g., germs, fungus, and dust) into the body. Pores located on the surface of the epidermis layer allow sweat, oil, and other excretions to escape from the glands embedded in the dermis layer. The excretion of these substances regulates body temperature and removes toxins from the body. In addition to glands, the dermis layers also consist of sensory nerves, which are responsible for a wide range of sensations, including pain, itch, pressure, temperature, vibration, and touch. The dermis blood vessels participate in thermoregulation, the transport of nutrients and oxygen, and the elimination of waste. Subcutaneous fat, which is the bottommost layer of the dermis, serves as a cushion, isolates the external environment, absorbs shock, and gives skin a supple appearance.

1.2. Causes of Burns and Pathology

A burn is a skin injury that can lead to tissue dysfunction. Thermal, chemical, and electrical burns are the most common types of burn injuries. Globally, over 300,000 deaths are caused by thermal or other kinds of burns each year. A high death rate exists because the management of burns is challenging. The most common complications include the loss of critical skin tissue functions, dehydration, wound infections, other systemic inflammatory responses, sepsis, and multiorgan dysfunction.

Thermal burn wounds can be attributed to several causes, such as sunburn (along with radiation burns), hot or boiling water, and, in the most severe cases, flames. In cases where there are fire hazards, the possibility of death is higher because of injuries related to the inhalation of toxic gases, such as steam.
smog, and other fumes. The Centers for Disease Control and Prevention (CDC) estimates that more than 450,000 outpatients within the USA are treated for burn injuries each year. The number of burn cases reached 486,000 in 2016. Despite the high demand for burn treatment facilities, there are only 127 specialized burn treatment centers available in the USA. The insufficiency and scarcity of treatment indirectly cause 3400 thermal burn-related deaths each year. Besides the shortage of medical care, other factors, including burn size, age, gender, and suffocation, also contribute to the severity of the injuries and the risk of death.

Apart from thermal causes, chemical exposure can also lead to burn injuries. Various chemicals and corrosives, such as strong acids and alkalis, hydrocarbons (e.g., gasoline and hot tar), and white phosphorus—a major ingredient in both armament and fireworks—can lead to skin burns. Chemical burns are often more severe than thermal burns. Chemical burns account for one-third of all burn-related mortalities and can cause further damage to skin tissue via chemical reactions and exothermic injuries. As the treatment for chemical burns is based on specific chemicals, the treatments required for these burns are more delicate and complicated than the treatment of thermal burns.

An electrical source is another cause of burns. When an electric current goes through skin tissue, it produces excessive heat and causes the body to reach fatal temperatures as high as 20,000 °C. Electrical currents can also cause fire in explosive or flammable objects. For example, clothes can be ignited, which further impairs the skin tissue from releasing thermal energy. There are three types of electrical burn injuries: low voltage burns (<1000 V), high voltage burns (>1000 V), and electric arc flash burns. The severity of electrical injuries is proportional to voltage. The most frequent high voltage burns within the United States are usually work-related, such as those observed in power line workers. A low voltage burn is less likely to result in tissue damage because there is less heat energy. Once the voltage exceeds 600 V, however, severe thermal burns can result and deep-muscle necrosis and amputation may be required for injury management. Lightning strikes are a unique classification of electrical burns that can lead to cutaneous burn injuries.

Once skin tissue is injured, some of the basic functions of the organ are affected or even completely lost depending on the severity of the burn. The compromised skin characteristics include cellular dysfunctions, hemodynamic and hematologic abnormalities, acid-base derangements, and hormonal alternations. Cellular dysfunctions are the result of the massive destruction of potassium transporters and sodium pumps. Damage to these systems leads to abnormal intracellular inputs of sodium and water and extensive extracellular potassium loss, which progressively causes systemic electrolyte disturbance and depression of cardiac output in patients with severe burns. In addition, cardiovascular functions, including the increase in systemic vascular resistance, the suppression of myocardial contractility due to the failure of aggressive volume resuscitation, the increase in hematocrit and blood viscosity, and the occurrence of the secondary anemia from erythrocytorrhexis, are affected. Acid-base derangement may result in metabolic acidosis in the early period of the burn injury. Hormonal alternations will aggregate at the wound sites by releasing various progressive substances, including histamine, kinin, oxygen radicals, and arachidonic acid, or by disturbing the neurohormonal axis.

### 1.3. Burn Classification

Skin thickness varies depending on age and location on the body. The thinnest skin is often found in infants or elderly people and the thickest skin is present on the palms of the hands, bottoms of the feet, and the back. These differences indicate that the severity of a burn can vary from mild to lethal, depending on the victim’s age as well as the location of the burn on the body. Burn injuries are traditionally categorized by degrees based on the severity of the injury (Figure 2 and Table 1). The first-degree burns include superficial burns, whereas burns of the fourth degree or higher include lethal burns. Currently, a modified classification system that categorizes burns according to the extent of tissue damage is preferred.
the requirement of surgical intervention has been widely accepted in burn management centers. The classification categories include superficial thickness, superficial-partial thickness, deep-partial thickness, and full-thickness burns. Superficial thickness (first-degree) burns only affect the upper epidermis layer, which is responsible for thermoregulation and infection prevention. Sunburn is the most common example of superficial thickness burns. Even though sunburns result from UV light rather than thermal trauma, the injured area immediately becomes red with erythema. The skin becomes dry and itchy after a few hours, but the epidermis is still intact and does not contain blisters. The symptoms subside after 7 days.

Superficial partial thickness (second-degree) burn injuries penetrate through the epidermis into the shallow dermis, which mostly consists of papillary connective tissues that serve to join the dermis and epidermis skin layers. Boiled water scalds and steam burns fall into this category. The epidermis is denuded and the papillary dermis is intact, and sensory nerves are not completely destroyed. Therefore, the pain is extremely deep red and exudate. The wounds heal within a month. The epidermis and dermis can be restored to a certain extent with some surgeries, but the outcome has limited plasticity.

Deep partial thickness (third-degree) burns damage deep dermis (reticular region) and sweat and oil glands. Hair follicle, sensory nerves, and capillaries are destroyed, but the nerve ending is still retained. The wound is serious but not extreme. The wound is pale, white, and to yellow. The healing time is 2 months. The wound is restored very slowly with plastic surgeries such as skin grafts.

Deep full thickness (fourth-degree) burns affect the entire skin layers and cause destruction of epidermis and dermis and charred skin tissue. The healing time is months, and the wound is permanent. The wound is restored by plastic surgeries such as skin grafts and multiple surgeries.

Table 1. Burn wound symptoms categorized by different degrees.

| Degree            | Depth                              | Blister | Pain             | Color                | Other                                      | Examples                  | Healing time | Scar       | Additional wound care                                           |
|-------------------|------------------------------------|---------|------------------|----------------------|--------------------------------------------|---------------------------|--------------|------------|---------------------------------------------------------------|
| Superficial       | Epidermis                          | No      | Yes              | Red (erythema)       | Dry, itchy, and hair shaft                 | Sunburns                 | 1 week       | No         | N/A                                                          |
| thickness (first) |                                    |         |                  |                      |                                            |                           |              |            |                                                               |
| Superficial       | Epidermis                          | Yes     | Exceedingly deep | Deep red             | Exudate                                   | Hot water scald           | 1 month      | No         | N/A                                                          |
| partial           | Shallow dermis (papillary region)  |         |                  |                      |                                            |                           |              |            |                                                               |
| thickness (second)|                                    |         |                  |                      |                                            |                           |              |            |                                                               |
| Deep partial      | Deep dermis (reticular region)     | Yes     | Very             | Pale white to yellow | N/A                                       | Boiled water scald, Steam | 2 months     | Permanent mild | Functional restoration surgeries—debridement surgeries/skin graft |
| thickness (second)|                                    |         |                  |                      |                                            |                           |              |            |                                                               |
| Deep full         | Entire epidermis, Dermis charred    | N/A     | No               | Charred, brown, and pale white | Leathery | Flame | Months | Permanent severe | Plastic surgeries—skin graft |
| thickness (third) |                                    |         |                  |                      |                                            |                           |              |            |                                                               |
| Fourth             | Entire epidermis, Dermis charred, Fats, Muscles, Ligaments | N/A | No | Charred | Coke-like skin tissue | Flame | Months | Permanent extreme | Multiple surgeries |

Figure 2. The degrees of burns and the corresponding damage on the skin caused by injuries. Higher degrees of burns indicate more severe injuries. The first-degree burns only affect the surface of the epidermis and cause redness. The Second-degree burns penetrate much deeper into epidermis and into part of the dermis and typically result in blisters. The Third-degree burns damage all skin layers down to the hypodermis, and the Fourth-degree burns destroy muscles, tendons, and bones. Reproduced with permission. Copyright 2018, Elsevier Ltd.
becomes deep red and wet causing blisters to form. The recovery time for superficial partial-thickness burns is around 1 month. A more extreme case of the second-degree burns, known as deep partial-thickness burns, damages the reticular region of the dermis layer along with hair follicles, oil and sweat glands, capillaries, and sensory nerves. The color of the wounds varies from pale white to yellow, and permanent scarring usually occurs. A meticulous skin graft is needed to restore the functions of the skin tissue in the case of deep partial-thickness burns.[2]

A full thickness burn, which is also called a third-degree burn, penetrates into all layers of the skin tissue and even permeates to subcutaneous tissues where nerves are located. As a result, these severe injuries are mostly painless. Full thickness burns cause the skin to become leathery. Because full-thickness burns are usually accompanied by other burns of different degrees, a wide range of colors, including pale white and brown, are often observed. In some cases, the skin is charred. To relieve the physiological stress brought about by scars, long-term plastic surgeries and skin grafting treatments are recommended during the post wound care periods.[3]

The different degrees described earlier are the most common burn categories, but the third-degree burns are not the most severe level of burn injury. If the victims are exposed to a heat source for a longer period of time, deeper burn wounds ranging from the fourth to sixth degree can arise. These burn injuries are more severe than the third-degree burns and are extremely lethal with a mortality rate of almost 100%. The symptoms of high-level burns are similar to those of the third-degree burns. The symptoms include the formation of charred tissues and permanent loss of tissue function due to the massive destruction of muscle and bone. In most cases, amputations are needed to protect a patient’s life. There are slight differences among burns categorized as the fourth, fifth, and sixth degrees. The fourth-degree burns extend underneath muscles and ligaments; the fifth-degree burns start to affect bones, and the sixth-degree burns completely char and destroy bone.

The degree of a burn is characterized by the depth of the wound; a higher degree indicates deeper burn injury.[15] In most clinical cases, however, the depth of a 3D burn injury is not homogeneous. It is often difficult to classify a burn injury using a single degree because the depth of the wound varies in the 3D environment. It is possible that some regions will have more severe symptoms than the rest of the wound. In addition, even after thermal irritants are removed from the injury site, a burn wound can remain in a dynamic state for up to 48 h.[16] As a result, deep-partial thickness wounds can become full thickness wounds if proper wound care is not provided or if edema forms.[17] The process for transformation of the second-degree burns to the third-degree burns is called burn wound conversion or progression.[18] In 1953, Jackson described three different burn injury zones. The three zones include the middle irreversible zone (coagulation), the surrounding damaged zone (stasis), and the outer curable zone (hyperemia). The prompt treatment of the middle stasis zone is critical for stopping the transformation of a second-degree burn to a third-degree burn. Delayed treatment of the stasis can lead to loss of perfusion and regression to irreversible coagulation.[19] Additional mechanisms that explain the connection and progression of the second-degree burns to the third-degree burns include microthrombosis,[20] necrosis,[21] and reactive oxygen species (ROS).[22]

The progression in burn wounds leads not only to deeper injuries but also to larger burn surface areas. Burn progression can further augment the complications of burn wounds by exacerbating scarring and loss of skin function, escalating pain and opioid use, and increasing the risk of morbidity.[18,23] Due to complex wound dynamics within the first 3 days and the unclear pathophysiology of the conversion process of burn wounds, it is often hard for medical practitioners to evaluate the degree of burn wounds and prescribe proper treatments.[24] While the underestimation of burn injuries can contribute to burn wound conversion, the overestimation of the severity of a burn injury can lead to unnecessary surgical wound treatments as well as hospitalization.[25] Considering the complications with burn wound assessment and treatment optimization, there is no cost-effective solution that can efficiently prevent the progression of secondary burn injuries. There is, however, a universal agreement that rapid debridement and topical antibiotic treatment are critical regardless of the mechanisms of conversion. Debridement is necessary, because necrotic tissue provides a suitable environment for bacteria to grow, erode, and worsen the condition of the wound.[18] Another common technique for preventing secondary burn progression is conducting immediate wound closure by auto skin grafting.[26]

1.4. History and Function of Burn Dressings

Wound healing typically consists of four consecutive and overlapping stages—hemostasis, inflammation, proliferation, and remodeling (Figure 3). During the hemostasis stage, which is also called coagulation, platelet plugs are produced to effectively stop wound bleeding, promote debridement, and prevent infection (Figure 3A). The hemostasis stage occurs right after a burn injury. During this period, growth factors, including platelet-derived growth factors (PDGFs) and transforming growth factors β (TGFβ), are released to attract inflammatory cells, such as neutrophils and macrophages, in preparation for an inflammatory response.[28] The burn wound starts to swell, which causes neutrophils and macrophages to gather within the fibrin clot—the scaffold allowing for the proliferation of endothelial cells within the wound defect. Neutrophils respond rapidly to germ invasions and are responsible for the clearance of microbes and debris.[29] Alternatively, macrophages, which differentiate from monocytes, can secrete vascular endothelial growth factor (VEGF) to stimulate angiogenesis and tissue granulation (Figure 3B). This process continues into the proliferation stage of endothelial cells when an eschar is gradually formed on the surface of the wound. In the meantime, keratinocytes migrate toward the wounded dermis under the eschar, and the fibrin clot becomes occupied by endothelial cells and fibroblasts around the newly formed vasculatures (Figure 3C). When fibroblasts differentiate into myofibroblasts, these contractile cells can gradually narrow the gap of the wound by producing extracellular matrix (ECM).[30] ECM is comprised of disorganized collagen, which pushes the healing process into the last stage—remodeling. The collagen in this stage is transferred from type III to type I, and the macrophages and neutrophils are gradually
removed from the wound tissues. The injured skin starts to restore tissue contraction and mechanical strength (Figure 3D).

To improve the wound healing process, dressings were invented as a temporary artificial skin.\[^{31}\] The wound dressing helps meet the demands of the three key requirements of wound care—debridement, infection prevention, and healing bed hydration.\[^{31}\] Wound dressings have been used for centuries dating back to prehistoric times. Around 2500 BC, the ancient Mesopotamians used clay tablets to stop constant bleeding after cleaning chronic wounds with milk or water. Around 1650 BC, during the times of the ancient Egyptians, soldiers discovered that covered wounds healed more quickly than open wounds. They used grease (e.g., gum, honey, lard, or resin) and wet gauze bandages made of linen or wool to cover wounds and prevent contamination. As recorded in Homer’s Iliad, which was written around 800 BC, wound dressings were used in the Trojan War by the ancient Greeks. Greek medicine was further influenced by other civilizations when Alexander the Great conquered Greece, Egypt, Mesopotamia, and India in 300 BC. By that time, the Greeks were stanching and antisepticising wounds with malachite, chrysocolla, and mercury. Their wound dressing methods were so successful that they were recorded in detail by Hippocrates (460–377 BC). Hippocrates was also the first person to record the process of chronic wound healing. He wrote that necrotic skin needs to be cleaned, and inflammation needs to be suppressed for better wound healing.\[^{32}\] Although they were successful, ancient wound treatments were experience-based and lacked support from scientific and systematic research on the biology and anatomy of the wound healing process.

Gauze is a traditional and well-established wound dressing that was first developed in the fifth century BC, as recorded by Hippocrates. Gauze is so simple and accessible that it is still widely used today. There are two types of gauze: traditional gauze made with 100% natural cotton cloth and modern gauze made from synthetic materials (e.g., rayon, synthetic blends, and polyesters).\[^{33}\] Gauze can be made simple and provides a medium for antibiotics, such as proflavine and chlorhexidine. It can strongly absorb wound fluids to maintain the appropriate amount of...
There are, however, some drawbacks associated with the use of gauze. First, woven gauze is absorbent and can easily stick to an eschar. Secondary trauma and pain associated with gauze removal are often unavoidable. Second, some threads or debris from the gauze can be left in wounds during gauze replacement. Third, because antibiotics degrade gradually, the woven structure of gauze allows for bacterial migrations after antibiotics deplete.\[13\]

To overcome the limitations associated with gauze, a new kind of semipermeable wound dressing made of cellophane film was developed during World War II to treat the second-degree burn wounds.\[15\] In comparison with gauze, this dressing effectively increases the healing rate of wounds and decreases the pain associated with dressing replacement. It also allows for water–gas permeation while preventing bacterial migration. Despite these benefits, cellophane is expensive, inflexible, and cannot be applied to burn wounds with complex 3D shapes.\[14\]

Continuous development in wound dressings has led to hydrogel-based dressings. Hydrogels are hydrophilic, macromolecular networks inherently cross-linked by polymer chain interactions.\[16\] The strong structural integrity of hydrogels allows them to hold up to 96% of water by volume without dissolving.\[17\] Hydrogels can be both elastic (solid) and diffusive (liquid) at the same time, which makes them applicable to various areas in biomedical research.\[18\] Moreover, hydrogels can reversibly respond to external stimuli, including temperature, pressure, and pH.\[19\] These characteristics render them tunable for biomedical applications.\[20\] Hydrogels can be designed to be nonirritating and nonreactive toward skin tissues and selectively permeable. Therefore, hydrogels are suitable materials for fabricating wound dressings. Hydrogel-based wound dressings can reduce the temperature of a wound by offering a soothing effect.\[21\] Compared with other types of dressings, hydrogels can facilitate the degradation of necrotic tissue, so that bacterial growth in debris is effectively hindered. The autolysis of bacteria and the act of sloughing can increase the healing rate of wounds.\[14\] In addition, the elasticity of hydrogels enables them to conform to wounds even if the injured tissues have complex 3D shapes. Moreover, hydrogels can be generated in a wide range of forms, such as sheets or gels, and be cut into different shapes according to specific needs.\[14\] The development of hydrogel dressings for burn wounds will be further discussed in the next section.

Other types of wound dressings have also been developed based on the evolving needs of patients. Some of the materials used to fabricate dressings include honey, iodine, silver, and soft silicone. In addition, bioactive wound dressings, medicated dressings, and composite dressings have been developed. The materials of construction, benefits, and drawbacks of these dressings have been summarized in Table 2.\[24\]

Dressing for burn wounds can be multifunctional to address specific needs. First, medications can be used to quench burn wounds and reduce pain by acting as an analgesic. This treatment can mostly be achieved by covering the wound with a moist saline-soaked dressing, which triggers local vasoconstriction and soothes the burning sensation of the wound. This cooling effect, however, does not necessarily eliminate pain, and further pain control is often needed.\[22\] The most common method for pain management is the intravenous injection of opioid drugs, such as morphine, fentanyl, and hydromorphone.\[2] Anxiolytic drugs are also sometimes considered. Second, the moisture level of a wound needs to be regulated. Moisture regulation accelerates necrotic tissue removal and the skin epithelialization process by 1) stopping the wound from bleeding and facilitating the clotting process; 2) stopping the leakage of plasma; and 3) absorbing other tissue fluids excreted from a wound.\[43\] Third, the dressing can also function as an antiseptic to enhance the speed of burn healing. Antibiotics reduce the formation of undesired bacterial colonies in wound beds, which facilitates the rate of healing.\[14,44\] The top antibiotic choice for burn wounds is silver sulfadiazine.\[45\] This antibiotic, however, is not applied to facial burns because the skin can turn gray after usage. The recommended antibiotics for facial burns are bacitracin or triple-antibiotic (neomycin, polymyxin B, and bacitracin zinc) composites. These antibiotics are less expensive and have the same efficacy as silver sulfadiazine.\[2]\ Mafenide and nitrofurazone are other antibiotic choices for burn treatment.\[46\]

Traditionally, a wound should be dressed after it is cleaned and debrided. Dressings should be replaced twice a day by gently wiping the residuals. The frequency of dressing replacement can be reduced when the wounds stop secreting exudates.\[2\] Considering the need to routinely replace wound dressings and prevent the detrimental effects of patient movement on wound recovery, an ideal wound dressing can be defined for burn treatment. An ideal dressing would (Figure 4): 1) be applicable to all wounds regardless of shape and location on the body, similar to ointments or sprays; 2) be elastic and elastic to adapt to body movement; 3) maintain an appropriate moisture level in the wound by absorbing the wound exudate and preventing dehydration or maceration; 4) maintain the appropriate temperature in the wound site by cooling down the burn to reduce the extent of burn trauma; 5) have appropriate adhesiveness—neither too tight to cause secondary injuries during wound dressing changes nor too loose to fall off frequently; 6) have adequate permeability to control water loss and allow for the diffusion of oxygen and carbon dioxide; 7) be analgesic, sterile, and biocompatible; 8) serve as an insulating cushion to prevent further trauma to the burn injuries from external factors, such as heat, water, and sunlight radiation; and 9) effectively cover the burn wound.\[41,47\]

2. Hydrogel-Based Burn Dressings

2.1. Prehospital Care for Burn Wounds

Effective and rapid treatment of burn wounds is expected to reduce the burn mortality rate, which currently stands at 4%.\[85c\] The mortality rate is high due to sepsis, organ failure, and other complications caused by intense inflammatory and immunological responses after a severe burn.\[2\] The complications associated with severe burn wounds can be controlled when outpatient care follows three phases: 1) prehospital care; 2) emergency department (ED) management; and 3) admission to specialized burn healthcare facilities.\[9\]

On-site, prehospital care is vital, because proper care immediately after an injury can significantly increase the chances of
| Dressing type | Trade name | Materials used | Pros | Cons | References |
|--------------|------------|----------------|------|------|------------|
| Gauze        | Kerlix     | Cotton fibers  | Cheap, accessible physical debridement, and impregnable | Sheds fibers, traumatic removal, and lateral bacterial migration | [101] |
| Semipermeable film | BAND-AID | Nonporous, plasticized polyvinyl polymer | Sterilizable, maintains moist environment, and prevents bacterial migration. | May not prevent maceration. | [35,102,129b] |
| Calcium alginate | CURASORB | Polymer extracted from seaweed | Absorbs excess moisture, prevents maceration, and sterilizable | Can shed fibers, requires moisture to ensure atraumatic removal, not suitable for dry wounds, and requires a secondary dressing | [103,130b] |
| Hydrogel     | Skintegrity hydrogel dressing | Cross-linked polymers, such as starch, cellulose, or other plant- or animal-derived polysaccharide | Can provide moisture to dry wounds as well as absorb excess exudate depending, Atraumatic when used correctly. Facilitates autolysis of necrotic tissue, and does not support bacterial growth | Only suitable for low exuding wounds or dry wounds. Can cause maceration in heavily exuding wounds, and can shift from dry to wet gangrene in exuding ischemic ulcers | [104] |
| Hydrocolloid | Medi-Pak Performance hydrocolloid dressing | Gelatin, pectin, sodium carboxymethylcellulose, and polysobutylene | Provides a moist, hypoxic wound environment | Does not prevent maceration in heavily exuding wounds | [105,129b] |
| Spray-on     | Nobecutane | Acrylic resin dissolved in acetic esters | Appropriate first aid and reduces infection in some surgeries | Possibly hemolyzing and difficult to achieve an even coating | [106] |
| Foam         | Tegaderm foam dressing | Polyurethane | Cut to shape, thermally insulating, provides moist interface, absorbs excess exudate, and impregnable | Not suitable for dry wounds | [107,130c,133c] |
| Capillary action | Vacutex 80% | Polyester with 20% cotton fibers, between two layers of perforated, permeable, nonwoven polyester | Decreases bacterial load on wound surface, assists in debridement and desloughing, and prevents maceration | Adheres to wounds with low exudate, possible traumatic removal. Adjunct contact layer required for arterial or heavily bleeding wounds | [108,130c,131c] |
| Odor absorbent | Carbonet | Incorporated charcoal or activated carbon layer within dressing | Retains odor-causing molecules and bacteria, impregnable with antimicrobial agents | Efficacy to retain odor and absorb exudate varies | [109,135a] |
| Scaffold—natural material | Alloderm (dermal substitute) | Acellular de-epithelialized cadaver dermis | Biocompatible, degradable, and is low in antigenicity | Collagen may enable the transmission of infectious agents and, thus, requires vigorous disinfection protocols | [110] |
| Scaffold—synthetic material | Integra (dermal substitute) | Silicone, collagen, and glycosaminoglycans | Variety of methods of construction, electrospray scaffolds stimulate cellular adhesion. Polylactides degrade to lactic acid ensuring limited host immune response. | Localized production of lactic acid may affect the efficacy of some proteins in the local environment | [110] |
| Honey dressing | Derma Sciences MediHoney | Medicinal honey, such as Manuka honey, incorporated into a hydrogel or alginate or applied topically | Antimicrobial, antifungal, anti-inflammatory, deodorizing, and prevents maceration | As a topical treatment, it rapidly dilutes and requires frequent dressings to maintain efficacy | [110,111d-f,134a] |
| Iodine dressing | Inadine dressings | Iodophors povidoneiodine (PVP-1) and cadexomer-iodine impregnated dressings | Antiseptic, only small amounts of free iodine released into wound site | Impedes wound healing through cytotoxic action against fibroblasts, Keratinocytes, and leukocytes; only suitable for short-term use | [112,133a] |
| Silver dressing | Sorbsan silver | Ionic, metallic, and nanocrystalline forms of silver have been used in the form of foams, hydrofibres, and hydrocolloids | Antibacterial action well established | Possible systemic toxicity currently being investigated; effectiveness varies between products | [113,133b] |
| Soft Silicone | Mepitel, Mepilex Ag | The contact layers consist of a polyamide net coated with soft silicone | Prevents maceration of the surrounding tissue, atraumatic removal with nonadherence to the wound site, suitable for wide range of wound types, can be used for difficult wound sites, can be left for up to 10 days, and can be impregnated with silver | Used in conjunction with secondary absorbent dressing and requires contact with the wound site | [114] |

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survival and decrease the level of scar synthesis, both of which are associated with wound dehydration and infection.\cite{56} One of the main purposes of prehospital care is to ensure patient safety and stability by 1) removing the burn clothes and hot ornaments to terminate heat exposure; 2) checking the accessibility of the airway and providing prophylactic intubations to prevent suffocation; 3) injecting analgesics and sedatives at the sites of injury; 4) performing debridement to remove dead skin, which is extremely vulnerable to infection and hinders wound healing; and 5) dressing the wound to protect it from bacterial infections, drainages, and ruptures. The second purpose of prehospital care is to initiate rehydration by administering an isotonic crystalloid solution intravenously.\cite{51}

Even when on-site treatment is administered, patients still need to be rapidly transferred to the nearest burn center for further treatment. Plastic surgeries and skin grafts are performed to facilitate healing of the burn wound when skin can be harvested from other parts of the body. Amputation is the most common option for burns beyond the fourth degree to remove extremities with function loss. Apart from physical management, the medical staffs in healthcare centers need to perform psychiatric evaluations of victims of self-inflicted burns to determine if they have suicidal tendencies. Psychiatric evaluations are also performed for accidental burns to gauge whether the victim suffers from post-traumatic stress disorder (PTSD). Hospitals also typically provide mental consulting to amputees.\cite{2}

2.2. Development of Sprayable Wound Dressings

All wounds differ depending on the wound healing stage, size, depth, and location. Thus, wound treatment is chosen on a case by case basis.\cite{49} Currently, a universal wound dressing that can be readily applied to all wounds does not exist.\cite{58} However, sprayable wound dressings,\cite{56} which can easily be applied to wounds without discomfort and can penetrate quickly and adequately into wounds, have been developed.

As severe burn wounds typically involve a large total body surface area (TBSA) and have a wide range of irregular shapes and depths, predesigned sheet-type hydrogel dressings are difficult to apply onto these wounds. Traditional hydrogel sheets need to be improved to reduce the time and material requirements of frequent, large-scale dressing replacements.\cite{52} In addition, slow dressing changes increase the risk of whole-body infection, which has a 75% mortality rate.\cite{53} Therefore, biodegradable, antimicrobial, and sprayable hydrogel dressings are suitable for burn treatment. These dressings can cover the wound surface and act as a temporary barrier. Compared with traditional dressings, sprayable dressings have greater exudate absorption\cite{52} and facilitate rapid and easy dressing application.

To design a suitable spray solution, it is critical to choose components with the desired characteristics. Specifically, shear thinning hydrogels are often desirable, so that the hydrogel can pass through the sprayer nozzle but also remain in the wound site without dripping. Carbomer, which is a common commercial thickening agent with a low viscosity, is often used in spray solutions. Carbomer has previously been demonstrated to have good compatibility with skin tissues and low toxicity.\cite{48} Polymerized gel-based Tisseel VH fibrin sealant spray delivery systems can also be used for burn treatment. This spray system consists of autologous multipotent mesenchymal stem cells (MSCs), which can be differentiated into fat, bone, or endothelium cells to cure wounds. The solution has a 5 mg mL\(^{-1}\) concentration of fibrinogen and thrombin. These proteins prevent the solution from dripping out of the wound site and help the polymer break down at a rate that allows for the release of MSCs for growth.\cite{55} In addition, research indicates that the fibrin matrix allows for fibroblast migration.\cite{56}

In addition to spray solutions, aerosol spray systems can be used in wound dressings. Compared with the sprays in liquid solutions, aerosols have better thermal stability, longer shelf life, and higher wound healing efficacy. When the aerosol is sprayed on the wound, it concentrates on the dressing contents in the injury site and acts as a protective film.\cite{51} Aerosol sprays are more suitable for dressings with enzymatic components, because some of the wound healing enzymes can deactivate in the solution state.\cite{57} An example aerosol spray, which included papain embedded pectin gel, was reported to soften dead skin and auto-debride necrotic tissue.\cite{57} Air or nitrogen can be used as

Figure 4. Functional characteristics of hydrogel-based wound dressing. Ideal properties of hydrogel dressings include flexibility to accommodate a wide range of movements and temporarily act as an artificial skin to block contaminate, such as water and bacteria. In addition, the hydrogel dressing can prevent excessive evaporation, absorb wound exudate, and allow for gas exchange to maintain appropriate moisture levels and oxygen concentrations in the wound bed. The image is created with BioRender.com.
an aerosol propellant for this new spray-on dressing. Nitrogen is superior to air, because air can negatively impact the enzymatic activity in wound healing. The thiolate ion groups (SO\(^2\) or SO\(^3\)) of papain, which serve as active sites for oxidation reactions, can be inactivated by air.\(^{[57]}\) Therefore, the half-life of nitrogen aerosol is ten times longer than that of spray solutions. In another study, a hydrophilic extract from the Haruan (Channa striatus), a kind of Malaysian fish, was used in aerosol sprays. This dressing was shown to stimulate wound healing and provide pain relief for full thickness burns.\(^{[51]}\)

In addition to liquid and aerosol sprays, solution blow spinning (SBS) is another promising method for dispensing hydrogel wound dressings onto burn wounds. In this approach, the hydrogel is deposited and applied to a wound site using a pressurized gas. By controlling the gas pressure, the ejection rate and the amount of hydrogel solution that is dispensed can be conveniently modified. Compared with aerosol sprays, the SBS method covers the wound with a fibrous and conformable scaffold and offers a healing environment with the proper porosity and moisture content. Similar to electrospinning, SBS generates nanofibrous wound dressings with high porosity. The nanofibrous porous structure of the dressings allows for rapid exudate absorption and oxygen delivery that is beneficial to the wound healing process. In one study, an SBS-based wound dressing was fabricated using a composite hydrogel that was made of biodegradable poly(lactic-co-glycolic acid), poly(ethylene glycol) (PLGA/PEG), and silver salt (AgNO\(_3\)).\(^{[52]}\) The high porosity of the wound dressing facilitated the sustained release of antimicrobial silver salts, which reduce the risk of infection.\(^{[52]}\)

Sprayable burn wound dressings are typically developed along with their injectable counterparts. A recent hydrogel-based sprayable wound dressing was reported to include a poly(N-isopropylacrylamide) (PNIPAM) hydrogel embedded with epidermal growth factor (EGF) and pH-sensitive silk fibroin/alginate nanoparticles loaded with the antimicrobial drug, vancomycin (VANC0).\(^{[58]}\) After spraying the hydrogel-based drug delivery vehicles onto the burn wound site, VANC0 was released in a controlled manner in response to pH. The drug was released faster in an alkaline pH but took up to 10 days to be released in a neutral pH environment. The release of AgNO3 from this hydrogel system took place over the course of 20 days. This wound dressing can be applied to the wound site in a sprayable or injectable form, and it can effectively prevent wound infections caused by S. aureus.\(^{[58]}\)

With the aforementioned advantages, sprayable wound dressings are promising for developing multifunctional hydrogel-based dressings with improved properties. There are, however, some engineering setbacks especially with the spray nozzles during the design of the dressing formulations. The main problems include the clogging of dispenser nozzles due to the high viscosity of hydrogel solutions and the generation of bubbles as a result of spraying.\(^{[59]}\) As a consequence, improvements in the technical design of spray dispensers are currently being investigated. Because the viscosity of the hydrogel is largely affected by concentration and molecular weight, the problem with dispenser clogging can be effectively solved by lowering the concentration and molecular weight of the polymer during the formulation design. For example, the highest polymer concentration that does not cause spray nozzle clogging for chitosan-based (medium molecular weight) wound dressings is 0.5% (w/v). The maximum concentration of the same biomaterial with a low molecular weight increases to 1.2% (w/v).\(^{[59]}\) Another solution for the problem of dispenser clogging is to heat the hydrogel solution before spraying it onto the wound site. To prevent the formation of bubbles during spray applications, the hydrogel solution can be mixed with antifoaming agents or plasticizers, such as glycerin or PEG.\(^{[59]}\)

### 2.3. Hydrogel-Based Dressings for Burn Pretreatment

The wound healing potential of hydrogels has been extensively explored and clinically studied since the 1980s.\(^{[36]}\) Hydrogel dressings meet the wound healing requirements listed in the previous section. First, natural hydrogel components, such as gelatin,\(^{[60]}\) hyaluronic acid, agarose, albumin,\(^{[61]}\) and alginate, are biocompatible, have low cytotoxicity, and are similar to ECM.\(^{[62]}\) These properties indicate that hydrogels are compatible with many different types of tissues. Biomaterials that are commonly used to develop sprayable hydrogel wound dressings are summarized in Table 3. Besides hydrogel composition, the cross-link density and mesh size can influence in vivo behavior, such as cell integration and tissue remodeling, and hydrogel properties, such as mechanical stiffness and degradation rate.\(^{[36,63]}\)

When hydrogel removal is needed, it can be degraded on-demand via different mechanisms (e.g., hydrolytic and enzymatic).\(^{[47]}\) Second, the semisolid hydrogels have unique mechanical properties including flexibility and elasticity. These properties allow the hydrogel to adjust to different wound shapes, fit to various locations on the body, and adapt to the complicated movements of patients. Third, hydrogels can absorb wound exudate and prevent the wound from dehydrating. This characteristic allows hydrogels to facilitate fibroblast proliferation and keratinocyte migration, both of which are essential steps in the wound healing process.\(^{[43]}\) Fourth, due to the high concentration of water within hydrogels, when clean running water is not accessible at an emergency scene, hydrogels can be used to decrease the wound temperature and prevent further burn damage. Fifth, the hydrophilic hydrogel surface provides an appropriate amount of adhesion to the wound. The hydrogel does not attach too firmly to the wound bed, which prevents disturbances to the growing cells and decreases the pain and discomfort experienced during dressing changes. Sixth, swollen hydrogels have a tight mesh size on the nanometer scale. The pore size is small enough to protect the wound bed from bacterial and fungal invasions\(^{[64]}\) while allowing for air and gas permeation. In addition, hydrogels are suitable 3D backbones for drug delivery systems. They promote wound healing\(^{[65]}\) by entrapping and gradually releasing biomolecules (e.g., cytokines and growth factors), pharmaceuticals (e.g., antibiotics, antiseptics, and analgesics), and cells (e.g., epithelial cells, fibroblasts, and stem cells).\(^{[36]}\) The chemical functional groups of the hydrogels can be modified to adjust cellular functions and adhesion.\(^{[36]}\) Seventh, the degradation process of hydrogels can be stimulated by hydrogel hydrolysis and cellular enzymes. The rate of degradation can be modified to match the rate of tissue regeneration. A slow degradation rate can impede wound closure, whereas a fast degradation rate can lead to the resorption of the premature scaffold.\(^{[36]}\) There is
| Hydrogel precursor | Active ingredients | Spray formation | Healing applications | Advantages | Degradation Experiment models | Treatment duration | References |
|--------------------|--------------------|-----------------|----------------------|------------|-----------------------------|-------------------|------------|
| N/A                | Ankerplast         | Solution spray  | Postsurgical wound sealing | Reduce wound infections | N/A Human patient | 56 days | [115] |
| PLGA/PEG           | AgNO₃             | Solution spray  | Total body surface area wounds | Prevent the high risk of infection | PLGA/PEG is ultimately degradable | Pig 35 days | [52] |
| Carbopol           | β-1,3/1,6-glucan   | Solution spray  | No specific           | Low viscosity, Low toxicity, High transparency | N/A Mice | 24 days | [116] |
| Chitosan/starch    | N/A                | Solution spray  | Ear/nose/throat surgical healing | Increased wound adhesion rate | N/A Sheep | 28 days | [117] |
| Agarose/gelatin    | N/A                | Dry gel spray   | Severe burns, diabetic, and decubitus ulcers | Restore the vascular integrity | Reduce scars and repair contraction | 10 h Rabbit | 4 weeks | [91] |
| N/A                | Hemoglobin         | Solution spray  | Crush wounds         | Increase the oxygen permeation to the wounds | N/A Pigs | 8–12 weeks | [73] |
| Chitin nanofibrils/ chitosan glycolate | –                | Solution spray  | Slow healing dermo epidermal wounds | Stimulate angiogenesis | Enhance dermo-epidermal lesion healing | N/A Wistar rats | 8–10 weeks | [118] |
| N/A                | Extraction of haruan (channa striantus) | Aerosol spray  | Full thickness burn | Stimulate wound healing | Pain relief | N/A Sprague-dawley rats | 21 days | [51] |
| Chitosan           | Autologous keratinocyte cells | Liquid spray  | Third degree burn | Stimulate fibrotic tissue formation | Fasten reepithelization | N/A Waster rats | 14 days | [84] |
| Alginate/hyaluronate | N/A               | Air propellant aerosol spray | Conceal the postsurgical peritoneal tissues | Careful hemostasis | Prevention of foreign body reactions | N/A Sprague-dawley rats | 7 days | [119] |
| Collagen           | LL37-SH peptides in AgNPs | Solution spray  | Chronic wounds with biofilm | Prevention of multidrug resistance | Anti-biofilms | N/A Mice | 4 days | [120] |
| Sodium hyaluronate/ carboxymethylcellulose | Sepraspray | Solution spray  | Anastomosed colonic wounds and intraabdominal incision healing | More applicable than the solid sheet in open and laparoscopic surgical circumstances | Higher regional efficacy with less toxicity | N/A Rat | 7 days | [121] |
| Pectin gel         | 0.1% w/v papain with SiO₂ particles | Nitrogen propellant aerosol spray | Ulcers, burn wounds, and postoperative wounds | The particles prevent the drug from dripping when applying vertically | The long half-life of enzymatic activity on the shelf | N/A Rabbit | 12 days | [57] |
| PEG                | SprayGel           | Solution spray  | Myomectomy             | Absorbable, flexible, and adhesive | Resorbed and cleared by kidney without toxicity | 5–7 days Human patients | 30 days | [122] |
| Acticoat           | Antibiofilm dispersinB enzyme | N/A Solution spray | Healing chronic wound with biofilm infection with MRSA | Enhanced antimicrobial by antibiofilm enzymes | N/A Mice | 2 days | [69] |

Table 3. Biomaterials that are commonly used to develop sprayable hydrogel-based wound dressings.
also another outstanding property, which gives hydrogels an advantage over traditional wound dressings (e.g., gauze and bandage). This property is transparency, and it depends on the polymer type and cross-link density of the hydrogel. Transparency allows for easy visualization of the wound during healing and enables treatment plans to be altered without having to replace the wound dressing.\textsuperscript{[36]}

### 2.4. Functions of Hydrogel-Based Burn Dressings

There are different types of wound dressings on the market for the second- and third-degree burns. A patch is the most traditional hydrogel wound dressing form, but opaque cream is frequently used to cover the gauze on wounds with eschar, exudative wounds, epithelializing wounds, or infected wounds.\textsuperscript{[66]}

Sprayable burn care is becoming more popular commercially because of its practicality. A spray formulation is suitable for first aid kits at offices and schools. Compared with other types of wound dressings, a spray can deliver a drug directly to the injury site without interacting with the gauze or other dressing media. The elimination of these interactions reduces waste, the possibility of infection, and pain during wound dressing changes. Sprayable drug delivery solutions evaporate on their own without any rubbing and leave a thin layer of drug film on the wound site. Considering these advantages, sprayable wound dressings are suitable choices for burn treatment compared with the other types of dressings, such as patches (Figure 5).\textsuperscript{[57]}

For all types of wound dressings, antimicrobial characteristics are crucial for improving healing. Since the American Civil War, soldiers have known that wounds can easily get infected and cause death if avascular dead tissues or foreign bodies are not debrided. The most effective way to minimize the possibility of infection is to perform debridement within 6–24 h after a wound occurs.\textsuperscript{[67]} Another example of the importance of timely debridement comes from the Vietnam War. In this war, helicopters often failed to take off on time because of fires or bad weather, and these delays led to a large number of casualties. In contrast, there was a significantly low number of wound-related infections after the Japanese attack on Pearl Harbor. The low infection rate was attributed to the prompt debridement of wounds using sulfa powder as suggested by the Hawaiian Department of Medical Officers.\textsuperscript{[46]} Since then, the use of antibiotics in burn wound healing formulations has become common practice.

If debridement cannot be done quickly after an injury, topical antibiotics need to be applied. While antibiotic treatment does not substitute for debridement, it can help prevent infection. When wounds are contaminated, the casualty rate can reach 80%, but with the proper use of mafenide or penicillin, the death toll can be reduced by 70%.\textsuperscript{[68]} Mendelson once conducted experiments on goats injured by an explosion. He surprisingly found...
that those treated with mafenide, a sulfa medication invented by Germany during World War II, were less likely to die compared with those who did not receive mafenide treatment. With this discovery, Mendelson and Lindsey invented a new hydrophilic ointment with this antibiotic for use in burn treatment.\[67\]

In more extreme cases, such as burn wounds with biofilm-embedded bacteria (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]), pathogenic bacteria can be inhibited and disrupted by applying an antibiotic agent. The combination of DispersinB (an antibiotic wound spray) and Acticoat (an antimicrobial) can enhance the antibacterial functions and improve wound healing compared with when an antimicrobial is used alone.\[69\] An antibacterial dextran blend hydrogel spray is another typical example.\[68\] The therapeutic efficacy of antibiotics such as gentamicin can significantly increase when encapsulated in hydrogel-based microparticles.\[68\] The microparticles prevent the burst release of the antibiotic in the wound and allow for sustained release over prolonged periods of times over 3 weeks. By modifying the antibiotic/hydrogel polymer ratio, the rate of antibiotic release can be further adjusted.\[68\]

A wide range of formulations have evolved to incorporate antibiotic functionalities in burn dressings. Compared with spray solutions, the release of antimicrobial drugs from hydrophilic ointments is relatively slow. The slow release rate may lead to inadequate drug concentrations within the wounds and allow for the growth of anaerobic bacteria. Unlike ointments, sprayable dressings evaporate rapidly after being applied to a wound. The antibiotics and bioactive molecules left behind are effectively absorbed by the injured tissues. In addition, the amount required for a sprayable dressing solution is relatively small (5 mL), enabling them to be portable and easily disposable. Therefore, sprayable dressings are suitable for practical applications especially in resource-limited settings.\[46\]

In addition to its ability to prevent infections, oxygen is also critical for the wound healing process, for controlling inflammation, angiogenesis, epithelialization, and remodeling. A lack of oxygen in the wounds, which is called tissue hypoxia, is the major cause of ulceration.\[70\] To prevent ulceration, sufficient oxygen must be provided to the wound. In most of the cases, the transudate can block the diffusion of oxygen into the wound bed. Therefore, proper wound treatment must maintain an appropriate amount of moisture in the wound while removing the diffusion obstacle for oxygen.\[71\] To address this need, a product that contains oxygen transporters in a sprayable dressing was developed. The external oxygen supply can compensate for the damaged vasculature within chronic wounds.\[72\] Based on this concept, a novel clinical approach has been applied to the treatment of chronic wounds. Hemoglobin, which is an important oxygen transporter, was incorporated into a sprayable dressing formulation. This spray can provide efficient oxygen delivery during the wound healing process, and it is natural and nontoxic.\[73\]

Examples of commercially available hydrogel-based burn dressings are provided in Table 4. The active ingredients used in these dressings have also been summarized in Table 4 along with the specific functions of each ingredient. Some of the active ingredients include external analgesics (e.g., benzocaine, lidocaine hydrogen chloride,\[74\] and benzocaine),\[75\] antibiotics (e.g., benzethonium chloride),\[76\] anti-inflammatory agents (e.g., glycine),\[77\] cooling agents (e.g., ethanol, which is also responsible for the evaporation), emollients, which are the first line of therapy used for treating scaling skin disorders and diseases (e.g., propylene glycol, which increases the capacity of skin to absorb water,\[79\] acetylated lanolin alcohol, zinc acetate, and vitamin B5),\[80\] and anti-burn healing agents (e.g., aloe vera or aloe barbadensis juice,\[81\] allantoin, lanolin, and dexamethasone). Specifically, dexamethasone is a nutritional element existing in the intracellular matrix that enhances healing abilities and suppresses inflammatory responses.\[82\] In addition, both allantoin and lanolin can accelerate cell regeneration and soften the stratum corneum, which is the outermost layer of the skin that functions as a barrier for water evaporation and external irritations.\[83\]

In addition to the traditional active ingredients found in commercial formulations, research labs have also focused on mixing cells with sprayable dressing solutions. For example, an autologous keratinocyte-embedded chitosan-based sprayable dressing was found to be suitable for the third-degree burn healing.\[84\]

Traditionally, patients suffering from high-degree burns are

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**Figure 5.** Synoptic scheme of the current and prospective use of hydrogels in burn wound care. Because of the tissue-mimetic characteristics of hydrogels, they have become the primary choice for developing wound dressings for burn treatment. Hydrogels have also been used to induce skin regeneration. Therefore, various types of regenerative hydrogels have been broadly developed. This trend enabled hydrogels to move from transient wound dressings to longer-lasting regenerative skin templates. Reproduced with permission.\[36\] Copyright 2014, Oxford University Press.
### Table 4. Examples of commercially available hydrogel-based burn dressings.

| Type               | Brand name                                      | Company                      | Burn classification           | Agents                                      | Degradable       | Function                              | Size  | Price  |
|--------------------|-------------------------------------------------|------------------------------|-------------------------------|---------------------------------------------|------------------|----------------------------------------|-------|--------|
| Spray              | WaterJel burn spray/first aid antiseptic         | Northern Safety & Industrial | Minor scald and burns         | Lidocaine HCl (2%) Benzalkonium chloride (0.13%) | Evaporate No rub in | External analgesic Antiseptic          | 2 oz  | $2.95  |
| Medi-first burn spray | Safetec of America, Inc.                          |                             | Minor scald and burns         | Propylene glycol (3%) Lidocaine (2%)         | Evaporate No rub in | Soothes and relieves skin Protection layer | 2 oz  | $2.19  |
| Health aloe extra instant burn relief spray | CVS Health                                     |                             | Minor scald and burns         | Lidocaine (0.50%)                           | Evaporate No rub in | Instant pain relief Instant cooling Moisturizing Itch relief | 4.5 oz | $7.29  |
| Solarcaine         | Walgreens                                       |                             | Sunburn and minor burns       | Lidocaine (0.5%) Aloe vera                  | Evaporate No rub in | Soothes and relieves skin Instant cooling Moisturizing        | 4.5 oz | $8.79  |
| Dermoplast pain relieving spray | Hospital strength                          |                             | Sunburn and minor burns       | Benzethonium chloride (20%) Benzocaine       | Evaporate No rub in | Anesthetic Antimicrobial Moisturizing | 2.75 oz | $12.49 |
| Dermoplast pain relieving antibacterial spray | Hospital strength                          |                             | Sunburn and minor burns       | Benzocaine USP (20%) Benzethonium chloride USP (0.2%) | Evaporate No rub in | Prevent skin infection temporary relief of pain and itching Instant cooling Instant pain relief Itch relief | 2.75 oz | $8.76  |
| Aspercreme lidocaine dry spray | Max strength                                   |                             | Sunburn and minor burns       | Lidocaine (4%)                              | Evaporate No rub in | Instant pain relief                      | 4 oz   | $8.99  |
| Panthenol ambulance for burns spray |                            |                             | Sunburn and thermal burns     | D-panthenol (dexpentanol) Pantothenic acid provitamin (vitamin B5) Allantoin | Evaporate No rub in | Reduces soreness Instant pain relief Prevent blisters Moisturizing Antiseptic | 130 g   | $16    |
| Biolex wound cleanser | Bard medical                                  |                             | First and second degrees of burns | USP purified water (65%) Aloe vera extract (30%) | Evaporate No rub in | Debris and slough soften and cleanser Wound washing | 6 oz    | $7.29  |
| Dermal wound cleanser | Smith & Nephew                                |                             | Minor scald and burns         | Polysorbate 20                              | Evaporate No rub in | Wound washing                           | 8 oz   | $8.98  |
| Restore wound cleanser | Hollister                                    |                             | Minor scald and burns         | N/A                                         | Evaporate No rub in | Wound washing                           | 16 oz  | $14.69 |
| Carrasyn hydrogel spray gel wound dressing | Carrington Lab                               |                             | First and second degrees of burns | Glycene Benzonic acid Butanamide Disulfurous acid Ethanol | Evaporate No rub in | Moisturizing                            | 8 oz   | $35.99 |
| | | | | | | | | | |
| DermoSyn            | Dermarete Industries                           |                             | First and second degrees of burns | Vitamin E                                   | Evaporate No rub in | Debris soften and cleanser Moisturizing         | 8 oz   | $11.95 |
| Equate burn relief spray | Equate                                          |                             | First and second degrees of burns | Lidocaine Diphenhydramine Aloe barbadensis leaf juice | Evaporate No rub in | Pain relief External analgesic         | 4.5 oz | $3.98  |
| Burnshield hydrogel burn spray | Burnshield                                    |                             | First and third degrees of burns | Tea tree oil (0.1%) Gelling agent (0.3%) | Evaporate No rub in | Sterile Absorbs and dissipates heat Minimizes burn damage | 1.8 oz | $3.18  |
| Burn relief first aid antiseptic/anesthetic spray | Zee                                             |                             | First and second degrees of burns | N/A                                         | Evaporate No rub in | Antiseptic Anesthetic                   | 2 oz   | $12.69 |
| Burn spray          | First aid only                                  |                             | First and second degrees of burns | Benzocaine Benzalkonium chloride             | Evaporate No rub in | Antiseptic Anesthetic                   | 4 oz   | $3.5    |
| Type         | Brand name     | Company                      | Burn classification                      | Agents                                      | Degradable | Function                          | Size   | Price    |
|-------------|----------------|------------------------------|------------------------------------------|---------------------------------------------|------------|-----------------------------------|--------|----------|
| Opaque gel  | Gentell hydrogel | Gentell                      | First and second degrees of burns        | Aloe vera extract                           | Evaporate  | N/A                               | 8 oz   | $10.99   |
|             |                |                              |                                          | Allantoin                                    | No rub in |                                    |        |          |
|             |                |                              |                                          | Polysaccharides                             |            |                                    |        |          |
|             |                |                              |                                          | Vitamins                                     |            |                                    |        |          |
|             | WaterJel burn gel | Northern Safety & Industrial | Minor scald and burns                    | Lidocaine HCl (2%)                          | N/A        | N/A                               | 3.5 g  | $24.3    |
|             | PluroGel       | Medline Industries, Inc.     | Third and fourth degrees of burns        | Phenoxethanol                                | 72 h       | Debris soften and cleanser         | 20 g   | $65.99   |
|             |                |                              |                                          | Sodium phosphate                            |            | Moisturizing                      |        |          |
|             |                |                              |                                          | Potassium sorbate                            |            | Protection layer                   |        |          |
|             | Restore hydrogel | Hollister                    | Second degree partial/full thickness     | N/A                                         | N/A        | Debris soften and cleanser         | 3 oz.  | $1.75    |
|             | AmeriGel hydrogel | AmeriGel                    | Second degree partial thickness          | N/A                                         |            | Prevent infection                  | 3 oz.  | $36.99   |
|             | DermaPlex      | MPM Medical, Inc.            | First and second degrees of burns        | Aloe vera extract                            | N/A        | Instant pain relief               | 6 oz   | N/A      |
|             |                |                              |                                          | Hyaluronic acid                             |            | Moisturizing                      |        |          |
|             | Flexderm       | Dow B. Hickam, Inc.         | First and second degrees of burns        | N/A                                         | N/A        | N/A                               | N/A    | N/A      |
|             | Curasol        | The Kendall Company         | First and second degrees of burns        | Hydrogel polymer                             | N/A        | Dyspigmentation                   | 3 oz.  | $4.66    |
|             |                |                              |                                          |                                            |            | Moisturizing                      |        |          |
|             | Carrasyn       | Carrington Lab               | First and second degrees of burns        | Glycine                                      | N/A        | Moisturizing                      | 3 oz.  | $32.07   |
|             |                |                              |                                          | Benzoic acid                                 |            |                                    |        |          |
|             |                |                              |                                          | Butanamide                                   |            |                                    |        |          |
|             |                |                              |                                          | Disulfurous acid                             |            |                                    |        |          |
|             |                |                              |                                          | Ethanol                                      |            |                                    |        |          |
|             | Hypergel       | Scott Health Care, PA        | First and second degrees of burns        | Sodium chloride (20%)                        | N/A        | Eschar and debris soften           | 0.5 oz | N/A      |
|             |                |                              |                                          |                                            |            | Extrudate absorbent               |        |          |
|             |                |                              |                                          |                                            |            | Moisturizing                      |        |          |
|             | NormGel        | SCA Hygiene Products, Eddy Stone, PA | First and second degrees of burns | N/A                                         | N/A        | Eschar and debris soften           | 1.5 oz | $25.63   |
|             |                |                              |                                          |                                            |            | Prevent infection                  |        |          |
|             |                |                              |                                          |                                            |            | Moisturizing                      |        |          |
|             | SoloSite wound gel | Smith & Nephew               | First and second degrees of burns        | Glycerol                                     | N/A        | Extrudate absorbent               | 3 oz   | $5.39    |
|             |                |                              |                                          | Carboxymethyl ether                         |            | Moisturizing                      |        |          |
|             | Transigel      | Smith & Nephew               | First and second degrees of burns        | N/A                                         | N/A        | N/A                               | N/A    | N/A      |
|             | GRX wound gel  | Geritrex Corp.               | First and second degrees of burns        | N/A                                         | N/A        | Pain relief                       | 3 oz.  | $5.51    |
|             |                |                              |                                          |                                            |            | Eschar and debris soften           |        |          |
|             |                |                              |                                          |                                            |            | Prevent infection                  |        |          |
|             |                |                              |                                          |                                            |            | Moisturizing                      |        |          |
|             | Intrasite      | Smith & Nephew               | Minor burns                               | Propylene glycol                             | N/A        | Facilitating autolytic debridement | 8 g    | $4.13    |
|             |                |                              |                                          |                                            |            | Extrudate absorbent               | 15 g   | $4.36    |
|             |                |                              |                                          |                                            |            | Rehydrate necrotic tissue         | 25 g   | $6.51    |
|             | NuGel          | Johnson & Johnson Medical    | First and second degrees of burns        | Sodium alginate                             | N/A        | Moisturizing                      | 25 mL  | $39.50   |
|             |                |                              |                                          |                                            |            | Facilitate autolytic debridement  |        |          |
|             |                |                              |                                          |                                            |            | Eschar rehydration                |        |          |
|             | Curafil        | The Kendall Company         | First and second degrees of burns        | Glycerin                                     | N/A        | Moisturizing                      | 0.5 oz | $4.66    |
|             |                |                              |                                          | Propylene glycol                             |            |                                    | 1 oz   | $6.83    |
|             |                |                              |                                          |                                            |            |                                    | 3 oz   | $9.67    |
|             | Patches        | Smith & Nephew               | First and second degrees of burns        | Polyacrylamide                               | N/A        | Transparent for easy monitoring  | 2"×2" | $2.51    |
|             |                |                              |                                          | Polysaccharide particles                     |            | Soothing and pain relief          | 4"×4  |          |
treated with autologous split-thickness skin grafts (STSG), which allow keratinocytes to proliferate in vitro. This method, however, is limited by the scarcity of skin donors. To tackle this problem, a new formulation of sprayable cultured single keratinocytes (CSK) has been developed to culture the keratinocytes in vivo. The sprayable CSK was mixed with chitosan gel, which promoted faster wound closure and fibrotic tissue formation and prevented cells from spreading by increasing the viscosity. Chitosan, however, failed to enhance re-epithelialization and granulation, which limited the application of this new burn spray.\[84\]

### 2.5. Technological and Regulatory Challenges for the Use of Hydrogel-Based Wound Dressings

Despite the promising potential and current developments in hydrogel-based wound dressings, there are pharmaceutical and regulatory requirements that need to be met. The intrinsic hydrophilicity of hydrogels might limit the amount of hydrophobic drug product and number of biomolecules that can be incorporated within the wound dressings for delivery applications. In addition, due to the dilution of hydrogel dressings by wound exudates, the stability, bioadhesion, and retention time of the wound dressings on skin tissue can be shortened.\[85\] These limitations can possibly be addressed by encapsulating liposomes within the hydrogel. Liposomes can dissolve in both hydrophilic biomaterials and hydrophobic drugs.\[86\] The combination of hydrogels with liposomes can also help improve the sustained drug release profiles during the healing process.\[87\] Moreover, the interactions between the charges on the surface of liposomes and hydrogels can enhance the biostability of wound dressings. In addition, these charges maintain the adhesiveness of the dressing formulations and extend the retention times. These properties are particularly useful for cases where a wound secretes large amounts of extrudate.\[85\]

The currently available scale-up strategies for hydrogel dressings are other technological challenges.\[86\] From an industry perspective, good manufacturing practices (cGMPs) need to be considered. These practices control the processes that are involved in the transportation, on-shelf storage, and sterilization of wound dressings.\[88\] The traditional synthesis methods for hydrogel-based wound dressings involve small batches, laboratory safety regulations, and therapeutic efficacy studies in large animal models. When the manufacturing process is scaled up to an industrial scale, batch variations could become more pronounced as a result of mass production. In addition, the potential heterogeneity of hydrogel polymers during large-scale production might cause safety and efficacy concerns in clinical trials.\[88\]

Government regulations, which are the end points for the commercialization process, might also limit the commercial availability of hydrogel-based wound dressing products.\[89\] Due to the use of different cross-linking agents to stabilize the dressing products, hydrogel-based wound dressings are subjected to additional regulations.\[88\] Unlike drugs, drug-embedded hydrogel-based wound dressings are mostly classified as either devices, permitted by Section 201g of the FD&C Act, or combination products, which require an additional 510(k) premarket notification submission review. This review can take 7–10 years for commercial approval by the Food Drug Administration.\[90\]

### 3. Future Perspectives and Applications

Burn wounds are generally difficult to manage. They typically come in a wide variety of shapes, are classified by various degrees, and lead to high mortality rates if not treated properly. Burn related mortalities typically result from fluid loss, large-scale infections, systematic inflammatory responses, or skin dysfunctions. Therefore, researchers have been designing and implementing novel wound dressings that can provide the required clinical treatment and decrease the number of deaths related to burn wounds.\[91\] An ideal burn wound dressing would be antibiotic and antiseptic, reduce scarring, provide moisturizing and pain relief, absorb exudate, act as a cushion, and serve as a wound healing drug delivery system. Secondary trauma caused...
| Burn degree | Hydrogel precursor | Active ingredient | Cross-linker | Advantage | Animal model | Treatment duration (days) | References |
|-------------|-------------------|-------------------|--------------|-----------|--------------|------------------------|------------|
| Partial thickness second degree | Gelatin | Hyaluronic acid Chondroitin sulfate | 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) coupling | Nanoparticles can act as antibiotics No cytotoxicity Facilitate re-epithelization, angiogenesis, and collagen fiber orientation Decrease the expression of TNF-α and increase the expression of MMP-2 in day 7 | Wistar rats | 28 | [126] |
| | | Asiatic acid ZnO nanoparticle (NP) CuO NP | | | | |
| | Collagen Polyvinyl alcohol (PVA) | Silver sulfadiazine- bFGF | Inherent self-cross-linking | Silver ion is effective in wound healing No skin irritation and dermal toxicity The benefit/risk ratio of silver salt is accessible for moderate burns | Guinea pigs | 14 | [127] |
| | Chitosan | Silver NP Aerva Javanica | Glutaraldehyde | Aerva javanica possesses antioxidant, antifungal, and antibacterial properties Aerva javanica can counter the cytotoxicity from silver nanoparticles The silver nanoparticle is an effective drug delivery system | Mice | 28 | [128] |
| | PVA Starch (St) Chitosan (Cs) | Zinc oxide nanoparticles (nZnO) | Freezing-thawing cycles | The tensile strength of the hydrogel can be modified by different ratios of the chitosan and nZnO The hydrogel with nZnO group is mostly absorbed in necrosis nZnO can improve wound healing The porous structures of the hydrogels allow the cells to migrate without any damage, proliferate, and grow The growth of hair follicles and glands can be facilitated | Rat | 14 | [129] |
| | Silk fibroin | bFGF liposome | Inherent self-cross-linking | bFGF can be sustained released in wound zone Increase the stability of bFGF inside of the body by encapsulating into the liposome Better cell proliferation in the skin tissue Angiogenesis promotion | Mouse | 14 | [130] |
| | Gelatin | Hyaluronic acid nanofiber | N/A Glutaraldehyde | Form more epidermis A smaller number of inflammatory cells | Wistar rats | 14 | [131] |
| | Glycerol monooleate Poloxamer 407 Aloe vera-based hydrogel | Silver sulfadiazine (topical antibacterial agent) | Gelling agent carbopol 934 Triethanolamine | Overcome the shortcoming of the commercial carrier base Aloe vera has anti-scar properties Least side effects | Rat | 30 | [132] |
| | PEG-LysSH Lysine-based dendritic macromonomers Thiol termination | Lysine-based dendriticN-hydroxyssuccinimide (NH5)-activated PEG-based cross-linker | On-demand wound dressing Atraumatic removal because of the thiolester exchange, better patient compliance | Wistar rats | 14 | [133] |
| | Antimicrobial carbopo Boron Poloxamer (F68 and F127) | | Inherent self-cross-linking | Increase wound closure, cell migration, cell viability, and gene expression Induced vasculization Antimicrobial effects Stimulate inflammatory responses | Mus musculus Second: 14; var. albino Third: 21 | [134] |
| | Second and third degree Chitosan-g-pluronic Nanocurcumin | | Inherent self-cross-linking | The nanocomposite hydrogel can combat a wide range of bacteria Higher collagen content Better granulation Higher wound maturity Easy to handle, transfer and applicable | | |
by frequent dressing changes is also a major concern. Thus, new burn dressings must also address this limitation.

Considering the advantages that hydrogel-based biomaterials possess, especially their high biocompatibility, low toxicity, appropriate degradation rate, drug encapsulation capabilities, and appropriate adhesiveness, hydrogels are a suitable option to use in wound dressings. Hydrogels have been utilized in a wide range of commercially available burn dressings ranging from opaque creams to patches. More recently, sprays have been introduced to the commercial market. Compared with patches, sprays can conform more easily to the shape of a wound. A main function of spray dressings is to increase patient compliance by significantly reducing the pain associated with dressing changes. Spray formulations maintain many of the functions of traditional hydrogels including drug delivery (e.g., drugs, small molecules, growth factors, and genes) and rapid gel formation due to fast cross-linking. Moreover, the viscosity and shear-thinning properties also allow the hydrogel solution to pass through a spray nozzle with an appropriate speed and remain in the wound without dripping. Another unique advantage is that the spray can evaporate quickly, and a swab is not needed to rub or remove the fresh gel residue during a dressing change. The elimination of swabs effectively reduces the chance of infection and secondary trauma. The simplicity and portability of spray solutions make them suitable for use in offices and schools during first aid emergencies. Inspired by a previously reported literature example by Madaghiele et al. (2014), Table 5 includes hydrogel-based dressings for the treatment of the second- and third-degree wounds.

### Table 5. Continued.

| Burn degree | Hydrogel precursor | Active ingredient | Cross-linker | Advantage | Animal model | Treatment duration (days) | References |
|-------------|--------------------|-------------------|--------------|-----------|--------------|--------------------------|------------|
| Full thickness third degree | N/A | Alpha keratose | Protein–protein interaction | Short wound healing duration | Yorkshire swine | 25 | [135] |
| Amniotic membrane (AM) | Silver nitrate | Gamma keratose | Inherent self-cross-linking | Short wound healing duration | Wistar rat | 21 | [136] |
| Electrospun nanofibrous silk fibroin (ESF) | Adipose-tissue-derived MSCs (AT-MSCs) | Inherent self-cross-linking | Scarless wound healing | Accelerate neovascularization | Mice | 28 | [137] |
| Silk fibroin | N/A | Inherent self-cross-linking | No additional cross-linking agents | Low cost | Mice | 21 | [138] |
| Starch/zeolite NP | Chamomile extract | Inherent self-cross-linking | The cross-linking method can be reached at room temperature and physiological pH | No cytotoxicity | Rat | 21 | [139] |
| Honey-chitosan-carbopol 934 | N/A | Chitosan and carbopol 934 | Natural and low toxic components | No persistent inflammation | Mouse | 9 | [140] |
| DexlEME | N/A | Inherent self-cross-linking | Appendages of the scars | Enhance neovascularization | Mouse | 35 | [141] |
| Dextran | N/A | Polyethylylglycol diacylate | Rapid wound closure | Enhanced ECM remodeling | Mouse | 40 | [142] |

4. Conclusion

Temporary wound dressings can effectively stop wounds from deteriorating in the pretreatment period when further grafting is under consideration by healthcare providers in EDs or burn centers. Massive burns destroy the skin tissue, and effective epithelization does not occur, especially for full-thickness burns. As a result, on-site pretreatment is not sufficient, and wound closure requires surgeries, such as excisions of burnt skin and donor grafting, to promote skin synthesis and angiogenesis. However, in practice, autografts are not always possible due to the lack of skin donors and the severity of the injuries. In addition, autographs typically bring about the unfavorable consequence of additional trauma and scars. Researchers are identifying new approaches to improve burn healing using hydrogels that can assist with skin grafts and promote skin synthesis and angiogenesis. Therefore, hydrogel-based regenerative dressings would be suitable for on-site pretreatment or for skin repair. The permanent skin substitutes are similar to multiple layers of natural skin and contain cultured exogenous cells that are released during the degradation of the biomaterial. By this design, skin regeneration and...
reinnervation\textsuperscript{[97]} can be achieved even though the new skin will not possess dermal appendages, such as hair follicles and glands.\textsuperscript{[98]}

Due to their simplicity and practicality, sprayable wound dressings are promising solutions for burn care and treatment. Despite many benefits, there are still some challenges that need to be addressed. Some of the main concerns include the effective and painless removal of sprayable dressings during dressing changes, development of products that have adequate thickness and prevent the spread and leakage of the gel matrix, and prevention of excessive bubble formation while spraying the dressing solution. These hurdles can be tackled using the principles of materials science, engineering, and biological sciences. Sprayable wound dressings are flexible and can easily be tuned and modified depending on the target application. For instance, changes in active ingredients allow the sprayable dressings to be used for chronic wound treatments such as in diabetic wounds. Alternatively, modifications in bottle and spray nozzle design can make the spray-on dressing suitable for resource-limited settings, such as battlefields. Sprayable wound dressings are promising products to treat burn wounds. They can also deliver drugs and biomolecules, which opens the possibility for new multifunctional products in the future.

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Conflict of Interest
The authors declare no conflict of interest.

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