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Case Report

# Biomaterials and Wound Healing: A Mini Review

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## Abstract

There are huge numbers of dressings available in the market for treating surgical site infections, wounds and burns worldwide involving multi billion dollars of investment. Dressing materials including hydrogels, electrospun mats, wound dressings incorporated with growth factors, skin substitutes derived from patients to promote wound healing mechanism are available currently. This article focuses on the established and recent advancement in the biomaterial fabrications for wound healing treatment and future directions in their development.

**Keywords: Surgical site infections; Biomaterial; Skin substitutes; Hydrogels**

## Introduction

Skin is the largest organ of the human body which acts as a barrier between the body and its surrounding environment. It exhibits first line of defense mechanism against microbial infection and protects the body [1]. Epidermis is the outer layer of skin that forms a tight junction for protection; it is made up of keratinocytes, melanocytes and Langerhans cells [2]. Beneath the epidermis is the dermis layer composed of collagen, integrins and laminin forming the Extra Cellular Matrix (ECM), the fibroblasts, mesenchymal stem cells, hair follicles, blood vessels, sweat glands and other growth factors and enzymes are embedded in ECM to maintain the skin environment [3]. The lowermost is the subcutaneous layer made up of adipose and connective tissue with sparsely spread collagen fiber and fibroblast cells [4]. This complex architecture of the skin is a challenging factor to replicate it in the laboratory (Figure 1).

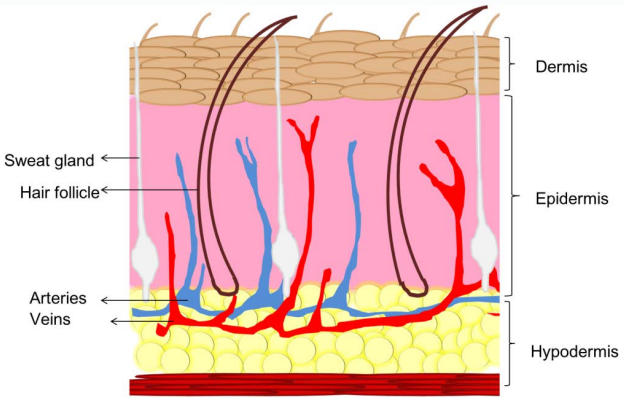


**Figure 1**: Normal skin architecture.

Any disruption in the normal tissues or organs underlying the skin, leading to severe damage is defined as a wound. It may occur because of physical, chemical, thermal, microbial or immunological disruption of tissues [1]. There are two types of wounds: acute and chronic, based on the mode of repair and healing process. Acute wounds generally caused by minor burns, mechanical and chemical injuries, heal in an orderly manner within a stipulated time period of 8-12 weeks [5]. Whereas, chronic wounds do not follow the orderly pattern of wound healing and the time limit, leading to delay in wound repair and serious scar formation [6]. The common chronic wounds are: Diabetic foot ulcer, venous ulcer, Arterial ulcer, Pressure ulcer, Pyoderma gangrenosum [7].

Wound healing is the process of tissue repair to restore its normal structural architecture and function after an injury [8]. The process involves the incorporation of inflammatory cells, increased collagen production and regeneration of epithelial cells for wound closure to occur [9]. The end product of wound healing is scar formationwhich is a dense connective tissue made up of collagen. Wound healing cascade is a complex and dynamic process involving four intricate and overlapping steps: Hemostasis, Inflammation, Proliferation and Maturation [10]. Through angiogenesis, fibroblasts along with other cells form granulation tissue followed by keratinocyte migration to close the wound which generally occurs during acute wound healing [11]. In case of diabetic wounds or burns the epidermis and dermis are extensively damaged where the repair process is more intricate and slows down the healing process eventually resulting in increased scar formation [1].

According to literature, around 13,000 operated patients in USA die each year due to Surgical Site Infections (SSIs). It is the most common Healthcare-Associated Infections (HAIS) comprising nearly 22% of the total population. Due to this postsurgical infection the postoperative hospitalization length is increased up to 10 days, with raise in the rate of readmission and death. Also, this infection costs approximately 10 billion US dollars annually towards the healthcare [12]. Hence for the management of chronic wounds, post-operative infections various numbersof dressing materials are available in the market [13]. Wound dressing materials includes hydrogels, electrospun mats, scaffolds made up of different materials possessing

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antibacterial property or biomaterials facilitating cell migration. Currently there are also other products available in the market, such as dermal substitutes, biomaterials incorporated with stem cells or other cells like fibroblasts and keratinocytes [14].

### Hydrogels

Hydrogels are promising wound dressing materials, as they maintain a moist environment around the wound surface, serves as a barrier from pathogens and also helps to promote wound healing mechanism [15]. Frequently, Polyvinyl Alcohol (PVA) is used in the fabrication of hydrogels for wound healing applications [16]. It is also used in combination with certain bioactive molecules like curcumin [17], zinc oxide nano particles [18], to fasten the wound healing rate. Like, PVA, Polyethylene Glycol (PEG), chitosan, collagen, alginate, agarose are also used in hydrogel preparation [15]. In a study, hydrogels healed pressure ulcers of a patient rapidly through accelerated epithelialization. In comparison with traditional wound dressing materials hydrogels have healed the wound faster with a healing rate of 85% [19]. The recent advancement in hydrogel is the injectable hydrogel formation with antibacterial activity that can be used for targeted drug delivery for complete coverage at the wound site [20].

### Electrospun fibre mats

Currently, electrospun mats are gaining interest in wound dressing material research as it enables easy gas exchange at the wound site and also the incorporation of hydrophobic active molecules, sustained release of drug is favorable. Fiber mats are produced using natural and synthetic polymers including collagen [21], polycaprolactone [22], gelatin [23], polyethylene terephthalate [24], along with biologically active molecules like silver [23], gentamycin [25]. The wound healing response is stimulated based upon the material used for fabrication [26]. Electrospun mats mimic the skin's ECM and hence it has the potential to accelerate wound healing.

### Skin substitutes

Through tissue engineering technique, skin grafts are produced for treating chronic wounds [13]. Currently, skin substitutes like dermal, epidermal, dermal/epidermal substitutes are in usewhich effectively mimic the ECM and are constructed using hyaluronan and collagen in addition toskin cells such as fibroblasts [27]. Though xenograft of bovine origin is useful owing to its low cost and availability, it is limited for human use [28]. To overcome this issue, recombinant protein production from human origin is increasing presently [29].

### Dermal substitutes

Fibroblasts are the major cells used in grafting, as they are typically found in skin ECM [30]. During tissue injury, fibroblasts differentiate into myofibroblasts for the synthesis of ECM components like collagen and fibronectin for the cells to proliferate and close the wound area [31]. In addition to this, they also secrete growth factors such as Platelet Derived Growth Factor (PDGF) to regulate the wound remodeling. Skin substitute secretes ECM components and forms a scaffold like structure inducing cell proliferation and maturation for the wound to heal. The fibroblast cells used in the skin substitute may be of patient (autologous) or allogenic (neonatal) origin [27]. However, the exact mechanism behind imitation of skin substitutes to fibroblasts of skin is not known. Further more research is required to understand this complex process.

### Epidermal substitutes

The epithelial cells provide highly specialized protection to the skin against external environment and maintain hydration of the skin [4]. Majorly, epithelial cell is made up of keratinocyte stem cells that restore the skin with new layers often. These newly formed cells form the outermost layer, the stratum corneum [32]. Hence these cells are used for the treatment of burn wounds as epidermal substitutes made up of sheets of cultured keratinocyte cells EpiCel™ [32]. In another study, keratinocyte cellwas genetically modified to incorporate wild-type gene LAM3B (laminin 332) to form a sheet of cells. This dermal sheet exhibited 80% similarity of natural skin ECM and when used for treating the wound it restored the skin architecture [33].

### Epidermal/dermal substitutes

Both keratinocytes of epidermis and fibroblasts of dermis region merge togetherduring general wound healing mechanism. This contact between these two cells is mediated by growth factors to restore the normal tissue structure [13]. In case of burns the dermis region is lost, which lacks fibroblasts, hence the healing mechanism is disturbed [34]. This has led to the epidermal/dermal substitute fabrication that contains both keratinocytes and fibroblasts to restore the communication between dermis and epidermis that mimics the normal skin framework [34]. In a study fibroblasts derived from collagen type-I of bovine origin and neonatal dermal keratinocytes was constructed to from an epidermal/dermal substitute called Apligraf® [35].

### Future directions

Skin is made up of a complex architecture comprising of dermis, epidermis layer and ECM that acts as a scaffold for cells to adhere and migrate with the involvement of growth factors. Any disruption in dermal or epidermal layer leads to wounds where it is difficult to recreate the complex architecture of skin. Hence, the current research in the advancement of biomaterials for wound healing treatment focuses on the development of biomaterial that closely resembles the skin structure. In burn injury the dermis and epidermis of the skin including hair follicles and sweat glands are diminished and it will not be completely restored during the normal healing process. Till now, no dermal/epidermal substitute that consists of the hair follicles and sweat glands cells are developed. And also biomaterial embedded melanocyte cells, that give color to the skinis also not yet developed. Hence, the next generation of wound healing therapy would focus on the incorporation of the stem cells into biomaterial that can differentiate into different cell lineages like fibroblasts, keratinocytes, melanocytes, hair follicles for a promising wound dressing material development.

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