

Advanced Therapeutic Dressings for Effective Wound Healing—A Review

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ABSTRACT: Advanced therapeutic dressings that take active part in wound healing to achieve rapid and complete healing of chronic wounds is of current research interest. There is a desire for novel strategies to achieve expeditious wound healing because of the enormous financial burden worldwide. This paper reviews the current state of wound healing and wound management products, with emphasis on the demand for more advanced forms of wound therapy and some of the current challenges and driving forces behind this demand. The paper reviews information mainly from peer-reviewed literature and other publicly available sources such as the US FDA. A major focus is the treatment of chronic wounds including amputations, diabetic and leg ulcers, pressure sores, and surgical and traumatic wounds (e.g., accidents and burns) where patient immunity is low and the risk of infections and complications are high. The main dressings include medicated moist dressings, tissue-engineered substitutes, biomaterials-based biological dressings, biological and naturally derived dressings, medicated sutures, and various combinations of the above classes. Finally, the review briefly discusses possible prospects of advanced wound healing including some of the emerging physical approaches such as hyperbaric oxygen, negative pressure wound therapy and laser wound healing, in routine clinical care. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 104:3653–3680, 2015

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INTRODUCTION

Overview

Wound healing is a global medical concern with several challenges including the increasing incidence of obesity and type II diabetes, an ageing population (especially in developed countries with low birth rates) and the requirement for more effective but also cost-effective dressings.¹ Wound healing is a complex process involving several inter-related biological and molecular activities for achieving tissue regeneration. The main physiological events include coagulation, inflammation, and removal of damaged matrix components, followed by cellular proliferation and migration, angiogenesis, matrix synthesis and deposition, re-epithelization, and remodeling.² These are generally classified into five major phases, known as hemostasis, inflammation, proliferation, migration, and remodeling/maturation.¹ Wound healing and the different phases involved have been extensively discussed in several reviews and textbooks and the reader is referred to these for detailed exposition on the molecular and physiological basis of the different stages of wound healing.^{1–9}

Wounds

A wound can be defined as an injury or disruption to anatomical structure and function resulting from simple or severe break in structure of an organ such as the skin and can extend to other tissues and structures such as subcutaneous tissue, muscles, tendons, nerves, vessels, and even to the bone.^{1,9,10} Of all the

body tissues, the skin is definitely the most exposed to damage and easily prone to injury, abrasions, and burns because of trauma or surgery. The rapid restoration of homeostatic physiological conditions is a prerequisite for complete lesion repair, because a slow and incorrect repair can cause serious damages including the loss of skin, hair and glands, onset of infection, occurrence of skin diseases, injuries to the circulatory system, and, in severe cases, death of the tissue.

On the basis of the nature of the repair process, wounds can be classified as acute or chronic. Acute wounds are usually tissue injuries that heal completely, with minimal scarring and within the expected time frame, usually 8–12 weeks.¹¹ The primary causes of acute wounds include mechanical injuries because of external factors such as abrasions and tears, which are caused by frictional contact between the skin and hard surfaces. Mechanical injuries also include penetrating wounds caused by knives and gunshots and surgical wounds caused by incisions, for example, to remove tumors. Another category of acute wounds includes burns and chemical injuries, which arise from a variety of sources such as radiation, electricity, corrosive chemicals, and thermal sources. Chronic wounds, on the contrary, arise from tissue injuries that heal slowly (normally do not heal within 12 weeks) and often reoccur.⁵ Chronic wounds are often heavily contaminated and usually involve significant tissue loss that can affect vital structures such as bones, joints, and nerves. Such wounds fail to heal because of repeated trauma to the injured area or underlying physiological conditions such as diabetes, persistent infections, poor primary treatment, and other patient-related factors.¹² These result in a disruption of the orderly sequence of events during the wound healing process.^{5,13,14} Furthermore, impaired wound healing can lead to an excessive production of exudates that can cause maceration of healthy skin tissue around the wound.¹⁵

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Table 1. Local and Systemic Factors That Slow Down Wound Healing⁷

Local Factors	Systemic Factors
Inadequate blood supply	Shock
Wound dehiscence	Chronic renal and hepatic failure
Infection	Advancing physiological age
Excess local mobility, such as over a joint	Obesity
Poor surgical apposition or technique	Smoking
Increased skin tension	Chemotherapy and radiotherapy
Topical medicines	Diabetes mellitus
Poor venous drainage	Systemic malignancy
Presence of foreign body or foreign body reactions	Immunosuppressants, anticoagulants, cortico steroids
Hematoma	Vitamin and trace elements deficiency

Wounds are also characterized based on the number of skin layers and area of skin affected.¹⁶ Injury that affects the epidermal skin surface alone is referred to as a superficial wound, whereas injury involving both the epidermis and the deeper dermal layers, including blood vessels, sweat glands, and hair follicles is referred to as partial thickness wound. Full thickness wounds occur when the underlying subcutaneous fat or deeper tissues are damaged in addition to the epidermis and dermal layers. Ferreira et al.¹⁷ have described both acute and chronic wounds that are difficult to heal as “complex wounds” with unique characteristics that can be summarized as extensive loss of the integument that comprises skin, hair, and associated glands; infection (e.g., Fournier’s gangrene) that may result in tissue loss; tissue death or signs of circulation impairment and the presence of underlying pathology.

Nawaz and Bentley,⁷ have described some of the factors that contribute toward retardation in wound healing (chronic wounds) that are summarized in Table 1. Common chronic skin and soft tissue wounds can be divided into three major groups because of similarities in their pathogenesis. These are leg ulcers (of venous, ischemic, or of traumatic origin), diabetic foot ulcers, and pressure ulcers.¹⁸ It also includes other hard-to-heal acute wounds such as wounds caused by cancer, pyoderma gangrenosum, immunologic and hematologic wounds,¹⁹ amputations, abdominal wounds, burns, and skin grafts.²⁰ In recent years, other more serious forms of chronic wounds such as buruli ulcer, caused by bacterial infection that involves significant skin tissue loss, have been reported.^{21,22}

Venous leg ulcers are triggered by malfunction of venous valves causing venous hypertension in the crural veins (veins supplying the leg), which increases the pressure in capillaries and results in edema. Venous pressure exceeding 45 mmHg certainly leads to development of a venous leg ulcer. Diabetic foot ulcer is triggered by monotonous load on the neuropathic and often ischemic foot, whereas pressure ulcers are caused by sustained or repetitive load on often vulnerable areas such as the sciatic (spinal nerve roots), tuberculum, sacral area, heels, and shoulders in the immobilized patient.²³ Patients with chronic ulcers usually present with underlying complicated factors caused by immunological defects, dysfunction in diabetic fibroblasts, and the effect of local infection or critical colonization and disruptive effects of bacteria. The resultant effect is increased cytokine cascades that prolong the inflammatory phase by continuous influx of polymorphonuclear neutrophils that

release cytotoxic enzymes, free oxygen radicals, and inflammatory mediators. These factors are responsible for cellular dysfunction and damage to the host tissue,²⁴ which cause delays or stop completely, the wound healing process.²⁵ The physiological basis of chronic wound evolution is complex. Continuous migration of neutrophils into the wound area causes raised levels of the destructive proteins called matrix metallo-proteinases (MMPs)^{26–28} including MMP-8 and neutrophil-derived elastase. This is in contrast to normal healing wounds in which excess levels of MMPs are inhibited through the non-specific proteinase inhibitor, α 2-macroglobulin, and the more specific tissue inhibitors of MMPs (TIMMP).²⁹ In chronic wounds, the ratio of the harmful MMP to the protective TIMMP is raised, resulting in the degradation of extracellular matrix (ECM),^{30–32} changes in the cytokine profile, and reduced levels of proliferative factors required for effective healing.^{33,34} Table 2 summarizes the different types of chronic wounds commonly encountered in clinical management, whereas Figure 1 shows photographic representation of the four most common chronic wounds reported.

The Need for Advanced Dressings

Wound dressings are traditionally used to protect the wound from contamination,³⁶ but they can be exploited as platforms to deliver bioactive molecules to wound sites. The use of topical bioactive agents in the form of solutions, creams, and ointments for drug delivery to the wound is not very effective as they rapidly absorb fluid and in the process lose their rheological characteristics and become mobile.¹ For this reason, the use of solid wound dressings is preferred in the case of exudative wounds as they provide better exudate management and prolonged residence at the wound site. Unlike traditional dressings such as gauze and cotton wool that take no active part in the wound healing process, advanced dressings are designed to have biological activity either on its own or the release of bioactive constituents (drugs) incorporated within the dressing.¹ The incorporated drugs can play an active role in the wound healing process either directly as cleansing or debriding agents for removing necrotic tissue, or indirectly as antimicrobial drugs, which prevent or treat infection or growth agents (growth factors) to aid tissue regeneration. In chronic wound management, where patients usually undergo long treatments and frequent dressing changes, a system that delivers drugs to a wound site in a controlled fashion can improve patient compliance and therapeutic outcomes. Bioadhesive, polymeric (synthetic, semisynthetic, or naturally derived) dressings are potentially useful in the treatment of local infections where it may be beneficial to achieve increased local concentrations of antibiotics while avoiding high-systemic doses, thus reducing patient exposure to an excess of drug beyond that required at the wound site.³⁷

Composite dressings comprising both synthetic and naturally occurring polymers have also been reported for controlled drug delivery to wound sites.¹ By controlling the degree of swelling, cross-linking density, and degradation rate, delivery kinetics can be tailored according to the desired drug release schedule.³⁸ Drug release from polymeric formulations is controlled by one or more physical processes including (1) hydration of the polymer by fluids, (2) swelling to form a gel, (3) diffusion of drug through the polymer matrix, and (4) eventual degradation/erosion of the polymeric system.^{37,39,40} Upon

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