A Comprehensive Review of Advanced Biopolymeric Wound Healing Systems

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ABSTRACT: Wound healing is a complex and dynamic process that involves the mediation of many initiators effective during the healing process such as cytokines, macrophages and fibroblasts. In addition, the defence mechanism of the body undergoes a step-by-step but continuous process known as the wound healing cascade to ensure optimal healing. Thus, when designing a wound healing system or dressing, it is pivotal that key factors such as optimal gaseous exchange, a moist wound environment, prevention of microbial activity and absorption of exudates are considered. A variety of wound dressings are available, however, not all meet the specific requirements of an ideal wound healing system to consider every aspect within the wound healing cascade. Recent research has focussed on the development of smart polymeric materials. Combining biopolymers that are crucial for wound healing may provide opportunities to synthesise matrices that are inductive to cells and that stimulate and trigger target cell responses crucial to the wound healing process. This review therefore outlines the processes involved in skin regeneration, optimal management and care required for wound treatment. It also assimilates, explores and discusses wound healing drug-delivery systems and nanotechnologies utilised for enhanced wound healing applications. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J. Pharm. Sci. 103:2211–2230, 2014

Keywords: wound healing; skin; wound dressings; bioactive agents; nanotechnology; extracellular matrix (ECM); polymeric biomaterials; tissue engineering; hydrogels

INTRODUCTION

The formation of creative ideas for the use and modification of delivery systems which will influence complex wound healing behaviours, such as proliferation, migration and differentiation of cells will promote novel opportunities for tissue regeneration and repair in the wound healing process. Many agents are pivotal and multifunctional, that is they are potent within the different stages of wound healing to ensure repair and regeneration.[1] Synthetic polymer delivery systems that can control and sustain release are particularly promising as materials for enhancing tissue regeneration.[2] This review discusses the processes involved in skin regeneration and the state of the art in nanotechnology and polymer drug-delivery systems and their potential application for wound healing. The interdisciplinary field of nanobiotechnology, which combines biology, chemistry, engineering and medicine is revolutionising the development of drug-delivery systems and devices. Research in the area of drug delivery, tissue engineering and wound healing has provided unlimited potential to improve human health.[3] Within the field of tissue engineering, drug delivery and wound healing, new dimensions can be envisioned with regards to enhancing the therapeutic effect and at the same time reducing risks and adverse effects. Developments in the field of nanotechnology involving nanomedicine, nanopharmacy, production of nanofibres, nanotubes and nanorods may promote novel opportunities for delivering wound dressings with efficient drug delivery.[4,5] Nanoscale delivery vehicles can enhance the therapeutic efficacy and enable new classes of therapeutics by encouraging the promotion of biologically active new molecular entities that were previously considered underdeveloped.[1]

PHYSIOLOGY AND MECHANISM OF ACTION OF THE NATIVE SKIN

The skin is the largest organ of the body which comprises about 8% of the human body mass and covers the entire external body surface. The surface area varies from person to person because of the variation in weight and height; skin thickness may also range from 1.5 to 4.0 mm.[6,7] The skin plays a crucial role in many functions such as sensory detection and fluid homeostasis.[8] It serves as an effective barrier against microbial invasion, and enables formation of a self-repairing and self-renewing interface between the body and its environment. It is capable of protecting the body against thermal, chemical, mechanical and osmotic damage, and has properties which allow for adsorption, selective permeability to chemicals and excretion.[7]

The main skin components of interest for wound healing comprises of the epidermis, dermis and sub-dermal layers (Fig. 1). The epidermis has a thin and highly cellular structure that forms the superficial layer of the skin. It is the outermost barrier having high impermeability, thus controlling water loss and serving as a barrier against external harmful stimuli. Underlying and separated from the epidermis by a basement membrane is the dermis. The dermis composes of collagen-rich extracellular matrix (ECM), elastin, fibroblast and glycosaminoglycans.[8] It provides flexibility and physical strength to the skin and supports the extensive vasculature, nerve bundles and lymphatic system. Throughout the dermis is a network of nerve fibres that serve a sensory role in the

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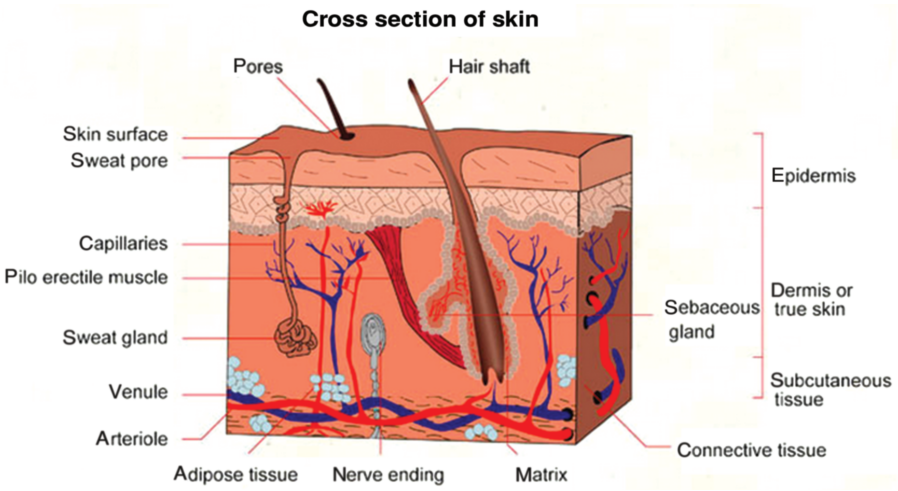

Figure 1. Image displaying the cross-section of skin.[6]

skin and influence immune and inflammatory responses.[7] The hypodermis is the layer beneath the dermis and contains a large amount of adipose tissue that is well vascularised and contributes to both the thermoregulatory and mechanical properties of the skin.[9]

WOUND TYPES AND THE WOUND HEALING CASCADE

A wound can be described as a defect or a break in the skin which could be due to physical, chemical or thermal damage or as a result of an underlying physiological or medical condition which would then result in a disruption of the normal anatomical structure and function of the skin.[10] Figure 2 classifies the various forms of wound occurrence, furthermore wounds may be classified as acute or chronic on the basis of the wound healing process. Acute wounds are usually healable within a period of time and are caused by traumas that would result in abrasions, avulsions, incisions, contusions and lacerations. These categories of wounds are likely due to by mechanical damage or exposure to extreme heat, irradiation, electrical shock or corrosive chemicals. Chronic wounds occur as a result of a specific disease such as diabetes, which could lead to ulcers, severe physiological contaminations and tumours. Unlike acute wounds, these wounds could take a long period of time usually exceeding 12 weeks to heal and reoccurrence is not uncommon.[11] Trauma to the skin is subsequently followed by the beginning of a regime of an organised and predictable sequence of events that has a cascade effect until the wound is bridged by scar tissue regeneration that binds and holds the wound in stasis.[12] The cascade of events initiated by skin trauma, involves three phases that is immediate and works towards repair as shown in Figure 3.

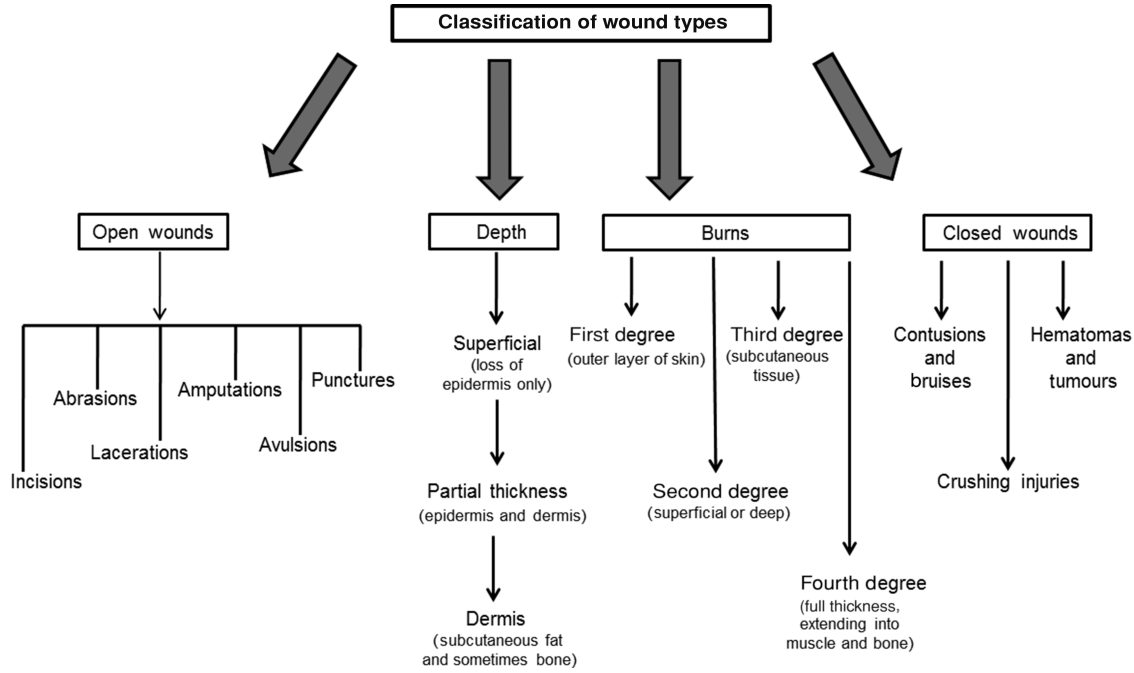

Figure 2. Classification of wound types.

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