Hydrogels as Biomaterials for Wound Dressings

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Wound management remains a challenging issue around the world, although a lot of wound dressing materials have been produced for the treatment of chronic and acute wounds. Wound healing is a highly dynamic and complex regulatory process that involves four principal integrated phases, including hemostasis, inflammation, proliferation, and remodeling. Chronic non-healing wounds are wounds that heal significantly more slowly, fail to progress to all the phases of the normal wound healing process, and are usually stalled at the inflammatory phase. These wounds cause a lot of challenges to patients, such as severe emotional and physical stress and generate a considerable financial burden on patients and the general public healthcare system. It has been reported that about 1–2% of the global population suffers from chronic non-healing wounds during their lifetime in developed nations. Traditional wound dressings are dry, and therefore cannot provide moist environment for wound healing and do not possess antibacterial properties. Wound dressings that are currently used consist of bandages, films, foams, patches and hydrogels. Currently, hydrogels are gaining much attention as a result of their water-holding capacity, providing a moist wound-healing milieu.

Keywords: chitosan ; cellulose nanocrystals ; hydrogels

1. Introduction

Wound can be defined as a damage of living skin or tissue [1]. According to various injury factors, wounds are known as: bruises, incisions, injuries, and cuts. It is mostly caused by external injury factors, namely surgery, external force, heat, current, chemicals, low temperature, and by internal factors such as local blood supply disorders. Wounds are classified as chronic and acute. Acute wounds can heal within 60–90 days depending on the nature (depth and size) of the wound [2]. Chronic wounds are wounds that heal significantly slower and fail to progress to all the phases of the normal wound heal process and are usually stalled at the inflammatory phase [3]. These wounds cause a lot of challenges to patients such as severe emotional and physical stress and generate a considerable financial burden on patients and the general public healthcare system. It has been documented that about 1–2% of the global population suffers from chronic non-healing wounds during their lifetime in developed nations. Traditional wound dressings are dry, and therefore cannot provide moist environment for wound healing and do not possess antibacterial properties [4]. Wound dressings that are presently used include films, foams, bandages, patches, and hydrogels. Nowadays, hydrogels are gaining a lot of attention as a result of their water-holding capacity, providing a moist wound milieu. Chitosan is a biopolymer that has received great attention recently in pharmaceutical industries because of its unique chemical and antibacterial nature. However, with its poor mechanical properties, chitosan is incorporated with other biopolymers to take advantage of desirable biocompatibility of chitosan at the same time having the improved mechanical and physical properties of the hydrogels. Naturally derived biomaterials such as carbohydrates have been employed to improve the mechanical properties of hydrogels. Cellulose is a highly abundant natural polymer which continues to attract a lot of attention until now because it is easily available, biodegradable and non-toxic [5][6]. Cellulose is usually incorporated with other polymers because it has a large surface area, non-toxic, excellent mechanical properties, biodegradable, and low density [7]. Although there are huge number of investigations based on the development of hydrogels from cellulose in various applications, the reinforcement of chitosan with cellulose materials in wound dressing continues to be of great interest. Furthermore, the encapsulation of therapeutic agents such as antibiotics, antioxidants, and growth factors and cells in hydrogels will enhance wound healing.

Hydrogels are three-dimensional network of cross-linked hydrophilic polymers which have the ability to absorb large volumes of water (water content can be up to 99%) [6][8][9]. The swelling ability of hydrogels is due to hydrophilic groups (-OH, -CONH-, -$CONH_2$, and -SO_3H) present in the polymeric components of the gels [10]. Hydrogels are derived from natural and synthetic polymers via physical or chemical crosslinking. The high-water content of hydrogels makes them compatible with most living tissues and thus facilitates widespread application in biomedical and pharmaceutical fields. For the past few years, investigators have focused their attention on the search for non-toxic and biocompatible materials for living organisms [11]. Over the past years, hydrogels have been used as drug delivery systems [12], wound dressings [9][13] gene transfection [14][15], tissue engineering scaffolds [16][17], and biosensors [18].

2. Types of Wounds

Wounds are of different types, which are caused as a result of physical, chemical, and thermal damages. Depending on the nature of the healing process, wounds can be divided into two main types, namely acute and chronic wounds [6][19].

Acute wound: an acute wound is an injury to the skin that takes place immediately rather than over time. Acute wounds in a normal healthy person will heal fast at the rate of the normal wound healing process because of a balance of growth factors, cytokines, and matrix metalloproteinase (MMPs) [20]. Basically, acute wounds can occur on any part of the body, which can range from superficial bruises to deep wounds causing damage to blood vessels, nerves, and muscles. Acute wounds may last up to 2 to 3 months followed by infection, pain, and necrosis [21]. Some examples of acute wound include (i) surgical wounds: Surgical wounds are incisions made intentionally by a medical professional and are cut precisely, creating clean edges around the wound. Surgical wounds may be closed (with stitches, staples or adhesive) or left open to heal by primary intention, (ii) traumatic wounds: These are unplanned injuries that can range from minor injuries such as a skinned knee, to severe injuries such as a gunshot wound. Examples of traumatic wounds consist of abrasions, skin tears, bites, and penetrating trauma wounds, (iii) burns: A burn is a type of injury to skin or other tissues caused by heat, cold, electricity, chemical, friction or radiation.

Chronic wound: it is a wound that fails to heal in a well-ordered set of stages and in an expected period of time of normal wound healing process. Wounds that take a long time (that is more than 90 days) to heal are generally considered chronic. Chronic wounds sometimes do not proceed to one or more of the wound healing phases. For example, chronic wounds are often stalled at the inflammatory phase for too long a period of time. Some of the common types of chronic wounds are diabetic foot ulcers, venous and arterial ulcers, and pressure ulcers [6][22]. Chronic wounds may take a very long period to heal or may never heal. These wounds cause severe emotional and physical stress, and pain in patients. Many factors are usually responsible for wound impairment. This is as a result of overlapping mechanisms in normal wound healing process that tends to prevent one factor from disrupting the process. However, when the healing process is disrupted and wound healing is impaired, this will lead to the development of chronic wounds. Generally, the main factors affecting chronic non-healing wounds include infection, imbalance in matrix metalloproteinases and matrix metalloproteinases inhibitors, oxidative stress, metabolic conditions, immunosuppression, and radiation.

Bacterial infection in wounds is the most often reason of the wound healing process interruption. Bacteria generate inflammatory markers that prevent the inflammatory phase as well as epithelialization phase of wound healing. The presence of bacteria in an infected wound leads to cell death, which causes an increase in inflammation response and persistent inflammatory phase. Necrotic tissues present in wounds disrupts the ingrowth of new tissues. In addition, necrotic tissue also serves as a ground for bacterial growth, leading to a pathologic cycle. When the bacterial burden of a chronic wound is more than 1×10^6 colony forming units per gram of tissue, it is considered as being clinically infected [23]. Commonly encountered, chronic wound bacteria include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Proteus* spp., *Streptococcus* spp., *Escherichia coli*, *Citrobacter* spp., *Morganella* spp. and *Corynebacterium* spp. Bacteria form protective biofilms that are not recognized by the host cells. Biofilms severely affect the wound healing process because they disrupt the immune response, prolong epithelialization, and decrease the growth of granulation tissues.

Persistent oxidative stress in chronic wounds disrupt inflammatory responses resulting in poor angiogenesis and re-epithelialization is impaired [24]. Oxidative stress is as a result of excess reactive oxygen species (ROS) production in the wound. ROS consist of hydrogen peroxide H_2O_2, superoxide anion O_2^- or peroxide O_2^{2-}. They are powerful oxidants and contribute enormously to cell damage, but they also play a vital role in the preparation of the normal healing process. Therefore, a balance between low and high level of ROS is very important. Low levels of reactive oxygen species are essential in the protection of tissues against bacterial infection and promoting wound healing by the production of cell surviving signaling [25]. There is no clear cut-off point for reactive oxygen species level in tissues but for normal wounds, the level of hydrogen peroxide (which is the most common oxidant) is in the range 100–250 µM [25].

3. Hydrogels as Biomaterials

Biomaterial is any material (synthetic or natural) used as a complete or as part of a biological system which has been impaired or to interact with living systems for medical purposes [26][27]. Biomaterial should be compatible and biodegradable. Biomaterials should not possess any kind of unfavorable or side reaction from the living tissue and vice versa. The biomedical applications of biomaterials include hip joints, drug carrier devices, bone plates, contact lenses, wound dressings [26]. Biomaterials such as gelatin, alginate, hyaluronic acid, dextran, elastin, collagen, cellulose nanocrystals, chitosan have gained great interest and are widely used for wound dressings and as drug delivery systems. Wound dressings are primarily produced from natural and synthetic polymers. In this research, the researchers focused on chitosan and cellulose nanocrystals as biomaterials for the development of hydrogels for wound management.

3.1. Gelatin

Gelatin is a natural biopolymer consisting of biologically active polypeptides derived from collagen in animal skin, bones, and other tissues. This polymer, being nontoxic due to its unique chemical and physical nature has been investigated as wound dressings and drug delivery systems [28]. Gelatin is also biocompatible, promotes cell adhesion and growth, non-immunogenic substrate of matrix metalloproteinases, and cost economy. Gelatin polymer consists of a large number of glycine, proline, and 4-hydroxyproline residues, which can have either acidic or basic properties depending on the extraction method [27]. Anionic acidic gelatin is useful for the delivering of positively charged bioactive agents whereas cationic basic gelatin is useful as drug system for negatively charged bioactive agents, forming polyion complexes. Its gelling properties can be controlled by chemical crosslinking with crosslinkers such as glutaraldehyde and genipin, that has been widely used for the development of wound dressings and as controlled release drug delivery systems. Gelatin has excellent property to form films, and thus is suitable material to produce capsules with rapid dissolution in gastric fluids. It is highly hydrophilic and has good swelling properties. Gelatin-based scaffolds have been used for a variety of biomedical applications, such as bone regeneration, skin tissue engineering [28], nerve tissue engineering, cardiac tissue engineering, tubular scaffolds, wound dressing and drug delivery systems [29]. Its application in drug delivery systems and wound healing is limited by poor mechanical properties. This disadvantage is overcome by the incorporation of other natural and synthetic polymers to reach the desirable biocompatibility and at the same time to have improved the mechanical and physical properties of nanofibers [29][30].

3.2. Cellulose

Cellulose is the most abundant natural polymer on earth, being the main structural component of plant cell walls. Cellulose has excellent characteristics, including recyclability, tunable surface features (**Figure 1**d), less risks of toxicity, biodegradability, biocompatibility [31]. Three types of nanocellulose are known, namely bacterial nanocellulose, cellulose nanocrystals, and cellulose nanofibers [32]. Bacterial nanocellulose is used for antibacterial wound healing and can safely and effectively improve wound healing [33]. Cellulose nanocrystals are excellent biomaterials with tunable surface chemistry. Recently, several studies have been focused on the topic of modification of cellulose nanocrystals, such as by esterification, oxidation [34], carbamation, amidation, etherification [35]. In the past years, it has been reported that cellulose nanocrystals can be oxidized with periodate and form several aldehyde groups [36]. The oxidation of cellulose with periodate leads to C2 and C3 carbon bond cleavage and aldehyde functional group formation on these carbon atoms. Therefore, dialdehyde cellulose nanocrystals may react with the free amino groups from chitosan or gelatin same as glutaraldehyde. This type of reaction is widely known as the Schiff base reaction [35].

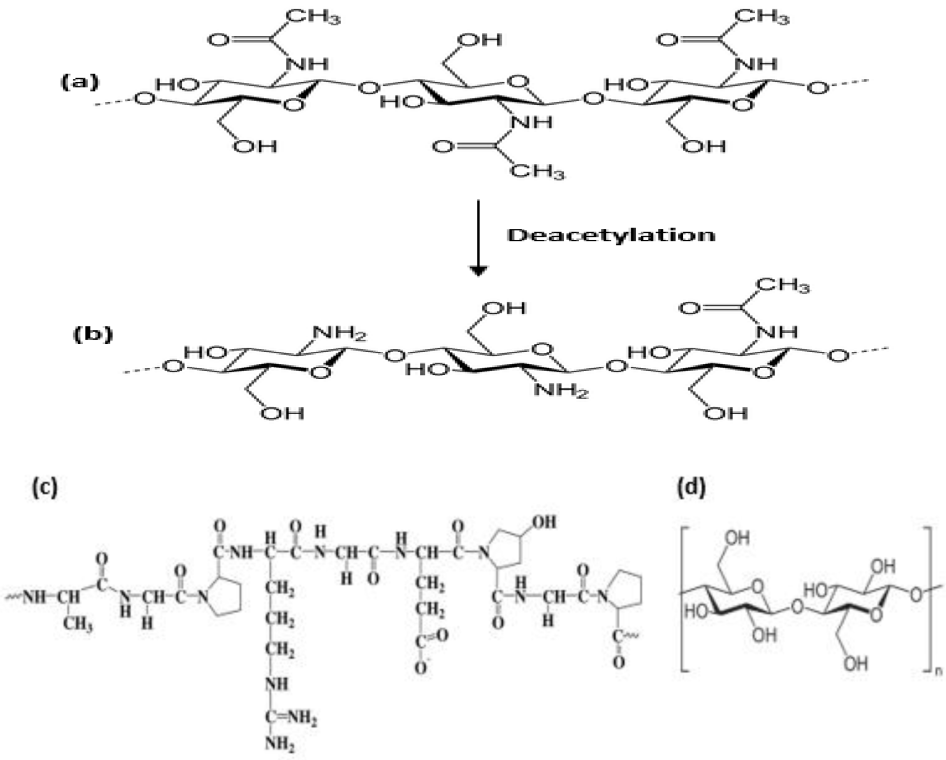

Figure 1. Polymer structure of (**a**) Chitin (**b**) Chitosan (**c**) Gelatin (**d**) Cellulose.

Zhang research group developed a well-reinforced chitosan/bacterial cellulose hydrogel, which demonstrated improved mechanical properties and bactericidal activity [37]. The in vivo study showed that the wound dressing with chitosan/bacterial nanocellulose was totally filled with new epithelial cells within a period of two weeks, with no significant side reactions.

3.3. Chitosan

Chitosan is a linear natural amino polysaccharide obtained by alkaline N-de acetylation of chitin (**Figure 1**a,b) commonly derived from exoskeleton of crustaceans such as crabs, shrimps and lobsters [38][39]. Chitosan and its derivatives are widely known due to their functionalities, being biocompatible, biodegradable, non-toxic, bio-adhesive, antimicrobial, antioxidant; and due to its wound healing properties is considered as an excellent material for wound dressings [33]. It can be used to form membranes, sponges, scaffolds and hydrogels. Hydrogel dressing due to the ability to provide optimal moist healing environment, can protect, interact, contract the wound, and facilitate wound healing [4]. Additionally, chitosan derivatives can easily be produced by chemical modification of hydroxyl- and amino-groups present in the biopolymer (**Table 1**). Some of these derivatives consist of N-carboxymethyl-, N-succinyl-, N-acyl-, N-carboxybutyl-, N-carboxyethyl-, 5-methylpyrrolidinone-, N-N-dicarboxymethyl-, O-succinyl-, and O-carboxymethyl-chitosan derivatives, etc. Chitosan has poor mechanical properties, and it can easily undergo deformation through external applied stress, but this challenge can be overcome by incorporating it with suitable polymers such as cellulose nanocrystals, to improve its mechanical properties for production of wound coverings [40].

Table 1. Some common modification of chitosan for wound healing dressings.

Modification	Properties
Carboxymethyl chitosan	**Improved solubility in water. The commonly explored derivative of chitosan; it is amphoteric in nature and its solubility depends on pH, when the pH is >7 it is water soluble.**
Thiolated urea derivatives	**Thiourea chitosan boost the antibacterial properties.**
Carbohydrate branched chitosan	**Water soluble. Carbohydrate can be grafted on the chitosan backbone at the C2 position by reductive alkylation. They could be used for wound dressing and drug targeting.**
Sugar derivatives	**N-Succinyl chitosan is an amphoteric polymer consisting of amine, hydroxyl, and carbonyl groups. It has excellent physical, chemical, and biological properties as required in biomedical applications.**
Alkylation chitosan	**It is an essential amphiphilic polymer based on polysaccharides. Improves the stability of the interfacial films, promotes its solubility.**

Chitosan is a biopolymer that is soluble in dilute aqueous acidic medium at a degree of deacetylation of 50% and higher (which depends on the origin of the polymer) as a result of its primary amino groups that have a pKa value of 6.3. The solubility takes place by the protonation of the amino group ($–NH_2$) of the D-glucosamine repeating unit, whereby the polysaccharide is changed to a polyelectrolyte in acidic media. Solubility of chitosan is commonly carried out in acetic acid by dissolving it in 1% or 0.1 M acetic acid [41]. **Table 1** summarizes some of the common modifications of chitosan along with their principal properties [42].

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