Chapter

Promising Hydrogels-Based Dressings for Optimal Treatment of Cutaneous Lesions

Ghica Mihaela Violeta, Cristina-Elena Dinu-Pîrvu, Lăcrămioara Popa, Elena-Emilia Tudoroiu, Diana-Georgiana Ionescu and Claudia-Maria Benga

Abstract

Worldwide, cutaneous lesions care represents a daily challenge for the medical system, with an increasing prevalence from year to year (from ~5 million in 2005 to about 8 million in 2018) and high costs for their treatment (between ~$28 billion and ~$97 billion). Injuries are the most frequent and destructive form of skin damage, affecting patients' quality of life. To promote wound healing, an ideal treatment involves proper dressings that can manage the local pain, inflammation, or infection. Passive or dry traditional dressings, such as cotton, gauze, or lint, have limited therapeutic actions and demand periodic replacement of the dressing. Therefore, an optimal alternative for advanced wound care is represented by hydrogels, one of the five classes of modern dressings, which assure excellent local moisture, due to their high ability to absorb a large volume of water inside their three-dimensional networks. Moreover, hydrogels possess suitable biocompatibility, biodegradability, porosity, elasticity, flexibility, and biological properties similar to the extracellular matrix. This chapter presents the main characteristics of the hydrogels and the recent research regarding the development of new hydrogel dressings, based on natural, semi-synthetic, or synthetic biopolymers, loaded with varied therapeutic agents to stimulate the tissue regeneration of different etiologies cutaneous lesions.

Keywords: different etiologies wounds, hydrogel dressings, wound healing, wound management, tissue regeneration, therapeutic agents sustained release

1. Introduction

With a length of ~2 m^2 and weight of ~15% of the body mass, the skin represents a sophisticated tissues complex of the human body, being the largest and the heaviest organ [1]. Due to its optimal physicochemical characteristics, the skin is a dynamic and effective outermost barrier, defending the body against the external surroundings [2]. In addition to the role of physical protection, the skin is involved in the regulation of the body's homeostasis, synthesis of vitamin D [3], and control of the temperature

and blood pressure. Furthermore, it impedes dehydration, maintains an optimal level of moisture and body nutrients, and exhibits self-healing properties [4]. Skin is also an essential sensory organ when it connects with the environment, and the stimulation is perceived on the human body as pain, temperature, and pressure [5]. Normal skin represents a stratified epithelium that is composed of three principal layers: epidermis, dermis, and subcutaneous tissue. The epidermis is made up of many cells, including melanocytes, Merkel, and Langerhans cells, but keratinocytes are the most numerous (~95%). This stratum has a thickness of 0.05–0.1 mm, and it does not contain blood vessels and sensory nerve endings [6]. Dermis represents a hard fibrous layer, due to its composition in collagen and elastic tissues. It is based on a supporting network that furnishes elasticity and toughness to the skin. Dermis exhibits a noticeable ability to absorb the water. Its thickness varies from 0.5 mm to 5 mm or more according to the skin region. Compared to the epidermis, the dermis is vascularized [7]. Hypodermis (subcutaneous tissue) represents the profound stratum of the skin, and it is made of fat cells among which are found elastin fibers, collagen, nerves, lymphatic, and blood vessels. The main roles of this layer are to store energy, to thermally insulate the body, and to defend against physical trauma [8].

Being the main organ that interacts directly with the environment, the skin is principally disturbed by external agents, such as chemicals, microorganisms, UV and electromagnetic radiations, allergens, heat, pollution, and mechanical trauma [9]. On the other hand, the skin can also suffer various modifications due to behavioral factors (smoking, alcohol, and nutrition), physiological factors (obesity), demographic factors (age and gender), and pathological factors (numerous local and systemic diseases) [10, 11]. All these mentioned factors often generate a skin injury and a delay in the healing process, so the restoration of healthy and functional skin is still a big challenge for the medical community [12] and an increasing problem worldwide [13]. Depending on the degree of the skin damage, cutaneous lesions can necessitate a long-term treatment, which involves a huge financial cost for global healthcare systems [14]. Statistics showed that the number of people with skin injuries of different etiologies worldwide is constantly growing from ~5 million in 2005, ~6 million in 2015 to about 8 million in 2018, and the total costs for their medical care are estimated to be between ~$28 billion and ~ $97 billion. Taking into account the dynamics of the factors that cause damage to the skin tissue, in the coming years, the total costs for their treatment are expected to rise [15, 16]. From all types of wounds, chronic lesions have the highest incidence in the population. Thus, in developed countries, approximately 1–2% of people will suffer a chronic lesion during their lifetime [17]. The highest increase is in the case of injuries caused by diabetes because it is estimated that in 2025 there will be at least 400 million people with diabetes globally, most cases being in South Africa, Asia, and Africa. About 15–25% of these people will develop throughout their life one of the major complications of diabetes which is the diabetic foot ulcer [18].

Most often a wound is accompanied by pain that can vary from mild to severe depending on the degree of the skin impairment. Hence, the personal life quality of the patients is considerably affected because they have to limit their daily activities, which negatively influences their physical, psychological, and social conditions [19, 20].

Optimal wound management needs physicians to comprehend the etiology of the wound, its healing time and complexity, the mechanism of injury healing, and the factors which affect the skin regeneration to make the right decision regarding the most efficient treatment for a proper cutaneous tissue restoration [21]. Since ancient

times, the care of a lesion involves its cleaning and applying a patch (traditional dressing) that allows protection from the external environment, but it cannot absorb high amount of exudates and requires regular application that produces soreness when changing the patch; moreover, the common patch owns modest adhesive characteristics and cannot furnish an adequate drainage for the injury. Consequently, the wound healing process is delayed, and the quality of the patient's life is seriously affected [22]. Nowadays, those patches have been switched with new wound dressings (modern dressings) that function as a physical and defensive barrier, swallowing the exudate and facilitating the healing process [23]. Over the last few years, modern dressings have been developed, which include hydrogels, hydrocolloids, semi-permeable films, foams, and alginates [24]. Comparing to the traditional dressings, these modern wound dressings, due to their improved structure, have a high capacity to generate a moist environment all over the skin lesion and to keep it, promoting the healing process and the reepithelialization by developing the proliferation of fibroblasts and enhancing the synthesis of collagen [25]. Moreover, they are semi-permeable and highly absorbent dressings and semi-occlusive or occlusive that stimulate the granulation tissue production and promote the epithelial cells movement from the injury margins to its center, providing an enlarged functionality [22].

Thus, this chapter highlights the main structural and functional properties of hydrogels, which are hydrophilic macromolecular networks, formed by crosslinking of diverse polymers, physically or chemically [26]. Also, this chapter presents recent studies regarding the broad applicability of hydrogels as bioactive dressings, which, after application to the wound bed and alleviate the pain, inflammation, and infection that generally follow a lesion [27]. Primary results consist of anatomical, functional, and esthetic restoration of the skin, improving the patient's quality of life [28].

2. Complexity of cutaneous lesions and skin regeneration process

Cutaneous lesions appear while the skin tissue is broken, or the cellular stability is imperiled under the action of physical, chemical, mechanical, and thermal agents or because of genetic diseases and metabolism-linked factors [29].

In the first instance, skin injuries can be clinically partitioned into acute and chronic injuries. Acute lesions are those wounds that often heal totally, with minimal scarring, in a period between 8 and 12 weeks [30]. Mainly, acute lesions can be produced by mechanical trauma; thus, these types of lesions can be classified inside one of these eight types: abrasions (it happens when a mechanical power scratches away a limited thickness of the skin) [31], avulsions (occurs when the primary layers of the skin are cut from the underlying fascia, for example, injury produced by animal bites) [32], contusions or bruises (fist leads to a contusion), crush wounds, cuts (knife or paper can cause a cut), fish hook injuries, incised wounds (it is the result of a surgical cut inside the skin) [33], and lacerations or tears (it means a break in the skin, which can be generated by a sharp object, for example, metal, glass, or wood) [34, 35]. Also, in the category of acute wounds are found burns and chemical lesions. On the other hand, chronic wounds heal slowly, their healing time exceeds 3 months, and they often reoccur. According to the Wound Healing Society, in this category of cutaneous lesions are included: pressure, venous, and arterial insufficiency, diabetic ulcers, and also malignant wounds [17].

Furthermore, from an etiological point of view, cutaneous lesions can be categorized as follows: surgical wound, which is a mechanical lesion produced by surgical

incisions, for example, to eliminate tumors [36]. Traumatic injury is an accidental and a spontaneous lesion that can vary from a small wound, such as a scraped knee, to a serious injury, such as a gunshot lesion. Abrasions, lacerations, skin tears, bites, burns, crush, and stab injury are some examples of traumatic wounds [37]. Radiation lesion is the result of radiotherapy and surgery, two treatment methods that are generally used for the therapy of cancerous tumors, lesions whose delayed healing produces physiological and psychological stress to the patient [38]. Chemical and thermal injuries (burns) are produced by a diversity of factors such as radiation exposure, electricity, corrosive chemicals, or thermal agents [39]. In these types of injuries, it is very important to know how deep the wounds are and how much of the body surface is affected, all these for good management that can lead to a decrease of wounds healing time [40]. According to World Health Organization, there are reported globally every year more than 11 million burn wounds and their medical care passes $12 billion per year [41]. A lesion becomes malignant when cancerous cells attack the epithelium, penetrate blood and lymph vessels, and invade the epidermis; mostly, this type of wound produces death and necrosis of the tissue [42]. Melanoma is metastatic skin cancer, with an increased risk of death, produced by uncontrolled growth of melanocytes that spread abnormally in neighboring tissues. This type of cancer produces severe wounds, requiring special treatment for optimum treatment [43]. Psoriasis is an autoimmune disease, characterized by erythematous-scaly lesions (crumbly white peels on irritated skin background) on the scalp, elbow, and knees, lesions to the face caused by sun exposure, and lesions at the level of the inguinal, axillary, or interfacial skin folds [44]. A pressure ulcer (pressure lesion, pressure sore, decubitus ulcer, or bedsore) is a surface of localized disturbance to the skin and hidden tissue, and it is induced by pressure, shear, or rubbing. The main risk factors that can lead to a pressure ulcer are incomplete nutrition, peripheral vascular disease [45], elderly people, obesity, diabetes, inadequate posture, pregnancy, smoking, or an increased frequency of infection (osteomyelitis) [46]. The most frequent complication of diabetes mellitus is diabetic foot ulcer, which affects 15–25% of diabetic patients. This is a condition that requires a long period for healing, or in some cases, it does not heal and can lead to infection, the major consequence being lower limb amputation [47, 48]. In close relation with diabetic foot ulcer is vascular ulcer, which is caused by disorders of the circulatory system; there are two principal types: venous ulcer (varicose ulcer) and arterial ulcer [49].

Based on contamination and postoperative infection risk, wounds can be classified in classes I, II, III, or IV. Class I or clean wound includes injuries that are infection-free, although current bacteria on the skin contaminate the injury [50]. Class II or clean-contaminated wound involves injuries, which affect the respiratory and digestive system, characterized by no loss of tissue fluid [51]. Class III or contaminated wound contains non-purulent inflammation and class IV or dirty/infected wound contains purulent inflammation [52].

According to appearance and injured tissue coloration, a wound can present necrotic tissue (characterized by a black or olive green coloration, often at pressure ulcer) [53], sloughy tissue (characterized by yellow coloration, related with excess exudates, produced during the inflammatory stage) [54], granulation tissue (characterized by red or deep pink coloration, typical for proliferative phase) [55], epithelializing tissue (characterized by pink coloration and formation of a new epidermis; it develops in migratory and proliferative phases) [56], and infected (malodorous) tissue (characterized by red coloration, hot inflamed tissue, pus formation, and unpleasant odor) [57].

An injury is classified according to complexity in simple and complex (complicated). A simple wound affects the skin tissue without any complication. On the other hand, a complex wound leads to a major tissue loss and a complicated wound involves an infected complex wound [58, 59].

Conforming to the depth of injury or number of skin layers affected, a wound can be superficial, partial thickness, or deep dermal and full thickness. A superficial wound is characterized by affecting only the epidermal skin surface, with minimum scars and a short period for healing, less than 10 days [60, 61]. A partial thickness or deep dermal wound represents a type of injury that affects the epidermis and also the inner dermal layers, containing blood vessels, sweat glands, and hair follicles; it requires between 10 and 21 days for healing, with the formation of scar and reepithelialization [62, 63]. A full thickness wound appears when hypodermis and also epidermal and dermal layers are damaged and the healing time is longer than the other two types of wounds (more than 21 days) [64, 65].

The regeneration of cutaneous lesions represents a fundamental physiological process that consists of a succession of cellular and biochemical events, which begin when a skin lesion occurs in order to reestablish the impaired tissue. The wound healing process involves more consecutive stages, but which still overlap: hemostasis, inflammation, proliferation, reepithelialization, and remodeling; therefore, skin tissue repair is one of the most complex processes that occur in the human body [66].

Multiple factors can delay the wound healing process, such as: different underlying physiological diseases (diabetes mellitus, human immunodeficiency virus, tumor resection, after organ transplantation, inborn genetic immunodeficiencies, burns, hypoxia, and vascular and autoimmune disease or cancer), obesity, continuous infection, stress, elderly population, sex hormones, gender, smoking, and malnutrition [67, 68]. Another cause for this delayed wound healing and epithelialization is represented by high levels of proteolytic enzymes and cytokines [69]. These factors lead to the production of a substantial amount of exudate [70], which decreases the mobility of lymphocytes and produces maceration of healthy tissue around the injury, the major problem which results being the inhibition of the wound repair process [71].

3. Bioactive hydrogel-based wound dressings

Traditionally, wound dressings have to protect lesions from physical impairment and secondary infection, to ensure thermal isolation, to be comfortable, and to be quickly changed by a new dressing, without producing any trauma on the lesion site, facilitating the dermal regeneration, playing a passive role in the evolution of the wound healing process [72]. Presently, these functions are constantly evolving. Medical healthcare systems demand for new "intelligent" products, which function not only as a protective barrier but also strongly promote the skin repair process [73]. Over the last few decades, there were developed numerous modern (advanced) wound dressings to stimulate the regeneration of cutaneous lesions, such as semi-permeable films and foams, hydrocolloids, alginates, hydrofibers, and hydrogels. These advanced products for optimal clinical management of skin wounds represent, in 2019, about $7.1 billion of the international market, and their manufacture is expected to increase to about $12.5 billion in 2022 [74]. Of all these modern products, the most competitive candidate is represented by hydrogels.

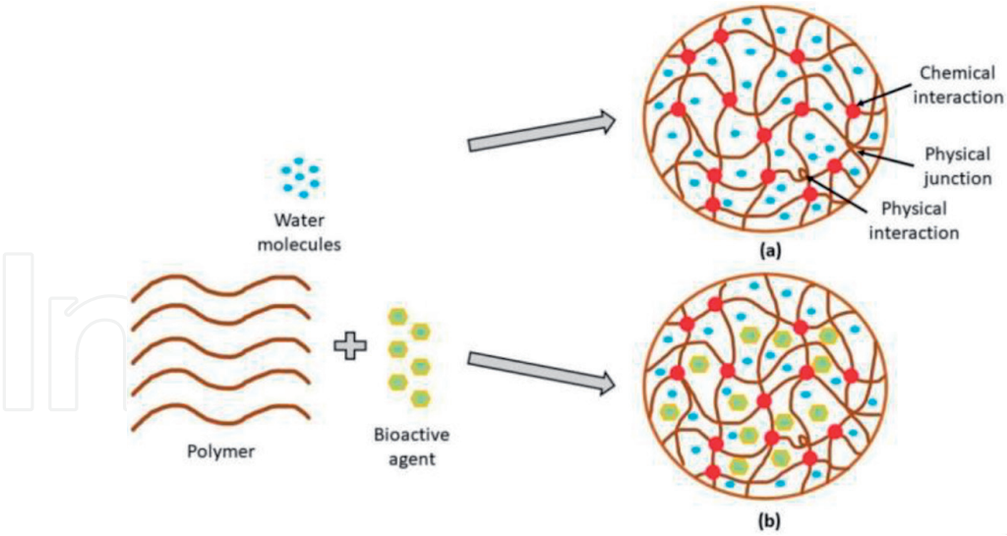

Figure 1.
Molecular structure of hydrogel: (a) without bioactive agent, and (b) with bioactive agent.

3.1 Molecular structure of hydrogels

Hydrogels, also known as aquagels, are a three-dimensional (3D) and crosslinked network of polymer chains, which can absorb massive quantities of water and body fluids due to their hydrophilic functional groups (hydroxyl, carboxyl, amide, and amino), adhering to the polymeric backbone [75]. The term "hydrogel" has been invented for the first time in 1894 by van Bemmelen. Due to their 3D structure, the molecular weight goes to infinity. The fundamental feature that characterizes the molecular structure of the hydrogel is the mesh size. There are two ways to crosslink the hydrogels: physically through hydrogen bonds and chemically through covalent bonds. The main property of the hydrogel is the super-absorbent capacity of water molecules that diffuse into the hydrogel network [76].

The molecular structure of hydrogel loaded or not with a bioactive agent is illustrated in **Figure 1**.

The swelling hydrogel includes three major phases:

1. Primary bound water—the molecules of water adhere to the hydrophilic moieties from the hydrogel structure;

2. Secondary bound water—the molecules of water combine with the hydrophobic moieties from the hydrogel structure;

3. Free water—the molecules of water totally swell into the empty spaces from the hydrogel structure.

The swelling ratio varies in accordance with polymers' content and the density of crosslinking [77].

3.2 Classification of hydrogels

Hydrogels products can be classified according to different measurable parameters as detailed below:

a. source: natural, synthetic, or hybrid (mixture of natural and synthetic polymers);

b. physical aspect: film, gel, matrix, or micro–/nanoparticles (microspheres) according to the method of the polymerization used in the preparation process;

c. dimensions: macro–/micro–/nanogel;

d. polymer composition: homopolymeric, heteropolymeric, copolymeric, hybrid, composites, or interpenetrating polymer network (IPNs);

e. network structure: permanent (chemical or irreversible crosslinking) or non-permanent (physical or reversible crosslinking);

f. preparation method: copolymerization, complex coacervation, irradiation, or using enzymes;

g. sensitivity to stimuli: physical (pressure, sound, temperature, light, and magnetic and electric fields), chemical (pH, molecular species, solvent content, and ionic strength), or biochemical (enzymes, antigens, and ligands) stimuli;

h. polymer network charge: amphoteric, non-ionic, ionic (cationic and anionic), or zwitterion (polybetaines);

i. chains configuration: non-crystalline (amorphous), semi-crystalline, crystalline, hydrogen-bonded, or hydrocolloids;

j. physical properties: smart or conventional;

k. biodegradability: biodegradable or non-biodegradable;

l. sensitivity to environmental factors: temperature, electric and magnetic fields, sound, enzymes, pH, or light;

m. equilibrium swelling grade (SWD): low (20–50%), medium (50–90%), high (90–99.5%—these hydrogels exhibit proper biocompatibility and permeability, which make them the most suitable for use in the medical domain), or superabsorbent hydrogels (>99.5%) [78–80].

Regarding the network structure, hydrogels are mostly manufactured from crosslinking networks, so there are two major categories of hydrogels: physically and chemically crosslinked hydrogels. Physically crosslinked hydrogels have gained importance due to the fact that they are easy to produce because no crosslinking agents are used during the synthesis process; thus, these types of hydrogels are used in biomedical, pharmaceutical, and food industries. Many methods are used to generate physically crosslinked hydrogels: freeze-thawing, stereocomplex formation, ionic interaction, hydrogen bonding, maturation (heat-induced aggregation), noncovalent interaction, and thermoreversible gels [81]. Chemically crosslinked hydrogels present covalent bonds in the middle of the polymeric network that generate permanent hydrogels formation. These types of hydrogels are formed through reactions between functional groups of polymeric chains. Many methods are used to generate chemically crosslinked hydrogels: condensation reactions, polymer–polymer crosslinking, high energy irradiation, enzymatic reaction, grafting, and radical polymerization [82].

3.3 Functional and technical properties of hydrogels

Hydrogels are of huge interest for the development of new wound dressings due to their outstanding mechanical and biochemical traits (biocompatibility, biodegradability, hydrophilicity, and the porous structure similar to the extracellular matrix) [83]. They are composed of 90 wt% water and 10 wt% different nature biopolymers. This high water content produces soothing and cooling effects, which reduce the perceived pain. Hydrogels stimulate the healing process through their moisture exchanging actions, which generate a proper microclimate between the dressing and the injury bed [74]. Depending on their composition, hydrogel-based dressings present a high power to swallow up to 1 kg of injury exudate per gram of dressing [84]. Thus, hydrogel-based dressings furnish optimal moisture on the lesion site, which has various advantages: to avoid the injury from drying out, to mitigate the pain perception, to damage the fibrin and dead tissues, and to allow the communication between target cells and growth factors [85].

Regarding the polymeric component, hydrogels can be produced from natural polymers (cellulose and its derivatives, collagen, hyaluronic acid, chitosan and its derivatives, gelatin, alginate, keratin, fibrin, pectin, elastin, dextran, chitin, and gums) and synthetic polymers (polyvinyl alcohol, polylactic acid, polyethylene oxide, polyglycolic acid, polyacrylic acid, poly ε-caprolactone, polyethylene glycol, polyacrylamide, vinyl acetate, N-vinyl-2 pyrrolidone, 2-hydroxyethyl methacrylate, methoxyl polyethylene glycol, ethylene glycol diacrylate, and poloxamer) [78, 83].

Hydrogels are colorless and odorless; they also exhibit the highest capacity to absorb fluids in saline medium, a high absorbency under load, low price, proper stability, and durability during the storage and in swelling conditions, neutral pH after swelling in water, nontoxicity, and photostability [75]. Hydrogels allow an excellent mechanical safety, a suitable gases exchange (CO_2 and O_2), the stimulation of angiogenesis, and the absorption of local exudates; thus, epithelial cells can flourish, and the healing process accelerates to restore the skin layers with minimal scars. Also, hydrogels exhibit non-adhesive characteristics, malleability, and smoothness, so they are easy to applicate and remove without tissue impairment [86].

Moreover, the transparent structure of these dressings allows a suitable evaluation of the wound healing progress, without the dressing being removed. Therefore, hydrogel-based dressings are the first option to treat dry, necrotic lesions, superficial

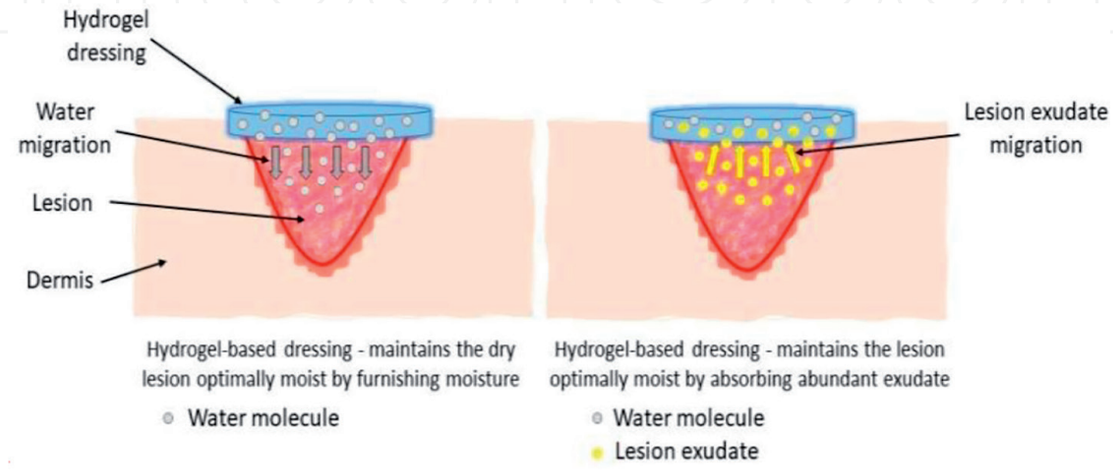

Figure 2.
The action mode of hydrogel-based dressing on cutaneous lesion for accelerating the wound healing process.

Type of lesion	Polymer composition	Bioactive agent/–s	Obtaining method/hydrogel type and properties	Ref.
Post-surgical lesion	Chitosan	Naproxen	Dissolution/thermosensitive; analgesic effect, postoperative adhesions treatment	[89]
	Polyglutamic acid/ pluronic F127	Paclitaxel	Double crosslinking/self-healing after surgical removal of melanoma, proper hemostatic effect, antibacterial activity, and mechanical properties	[90]
	Poloxamer 407/sodium hyaluronate	Ropivacaine	Physical blending/thermosensitive; analgesic effect, efficient long-term pain alleviation	[91]
Radiation-induced lesion	Carbopol	Sildenafil citrate	Physical blending/notable wound contraction, minimization of skin impairment, excellent tensile strength, enhanced production of granulation tissue, mature collagen fibers, and less inflammatory infiltrates	[92]
	Alginate/hyaluronic acid/polylysine	Curcumin and epigallocatechin gallate	Crosslinking/angiogenesis stimulation, inflammation relief, and reactive oxygen species (ROS) scavenge	[93]
Burns	Alginate	Vancomycin, gentamicin, or minocycline	Physical blending/infection treatment and burn depth reduction	[94]
	Chitosan	Gold nanoparticles and Aerva javanica	Crosslinking/antimicrobial and antioxidant activities	[95]
	Keratin	Ciprofloxacin	Physical blending/antibacterial effect, collagen deposition, tissue remodeling, and macrophage recruitment	[96]
	Hydroxypropyl methylcellulose/ hydroxyapatite	Silver nanoparticles	Crosslinking/3D porous network, high antibacterial, mechanical, optical, and spectral properties, proper swelling and degradation ratio, wound closure improvement with rapid reepithelialization, and minimal scar tissues	[97]
Pressure ulcer	Chitosan	Genipin	Crosslinking/pH-responsive; antimicrobial, hemostatic, and mucoadhesive characteristics, wound site pH neutralization, and high swelling capacity	[98]
	Polyvinyl alcohol	Poly(lactic-co-glycolic acid) nanoparticles loaded with ciprofloxacin hydrochloride	Crosslinking (gamma radiation)/antimicrobial activity, good gel fraction, and excellent swelling ability	[99]
	Gelatin/silk fibroin	Growth factors (adipose-derived stem cells and platelet-rich plasma)	Photocrosslinking (UV light)/optimal swelling ratio, rheological and mechanical properties, rapid reepithelialization and collagen deposition, inflammatory infiltration decrease, increased angiogenesis, and nerve regeneration	[100]

Type of lesion	Polymer composition	Bioactive agent/–s	Obtaining method/hydrogel type and properties	Ref.
Venous and arterial leg ulcers	Chitosan	Gallic acid	Enzymatic crosslinking/antibacterial and antioxidant activity, inhibition of matrix metalloproteinase, myeloperoxidase, and collagenase	[101]
	Pluronic F-127	Antisense oligodeoxynucleotides	Crosslinking/thermoreversible; anti-inflammatory effect (neutrophil cell infiltration reduction)	[102]
	Polyvinyl alcohol/ chitosan	Ibuprofen-β-cyclodextrins	Physical blending/macroporous network, optimal mechanical and morphological properties, anti-inflammatory effect, and scab formation prevention	[103]
Diabetic foot ulcer	Alginate	Polydeoxyribonucleotide	Crosslinking/stimulation of cell promotion and angiogenesis	[104]
	Gelatin methacryloyl	Cerium-bioactive glass	Photocrosslinkin/proper swelling ratio, cell adhesion, compressive features, antibacterial activity, granulation tissue formation, increased angiogenesis, and collagen deposition	[105]
	Hydroxypropyl methyl cellulose	Valsartan	Physical blending/antimicrobial effect, decrease of the level of the proinflammatory factors	[106]
	Chitosan/hyaluronic acid	Insulin glargine	Crosslinking/pH-responsive; inflammatory phase reduction, enhanced collagen deposition, granulation tissue production, reepithelialization, neovascularization, and peripheral neuropathy	[107]
	Poly(ε-caprolactone)/ poly-(glutamic acid)	Ciprofloxacin	Physical blending/inhibition of superoxide free radicals and high antibacterial effect	[108]
Psoriatic lesion	Carbopol	Apremilast	Crosslinking/proper anti-inflammatory effect (reduction of TNF-α level) and mechanical properties	[109]
		Methotrexate	Physical blending/anti-inflammatory effect, proper viscoelastic and bioadhesive behavior	[110]
		Clobetasol propionate	Crosslinking/anti-inflammatory, antioxidant, and immunomodulatory properties, pseudoplastic behavior, spreadability, and mechanical properties	[111]
	Pluronic F-127	Cyclosporine	Physical blending/suitable mechanical properties, viscosity, and pH, reduction of hyperplasia, and tissue impairment	[112]
	Pluronic F-127/ hyaluronic acid	Curcumin	Physical blending/optimal anti-inflammatory activity and mechanical properties	[113]

Table 1.
Recent studies regarding the development of new hydrogel dressings based on different polymers composition and bioactive agents for tissue regeneration.

injuries (burns and skin tears), surgical wounds, radiation burns, sloughy and dehydrated lesions, and shallow ulcers. Depending on the hydration level required by the lesion, hydrogel dressings need to be changed every 1–3 days [87]. The schematic illustration of the action mode of a hydrogel-based dressing on cutaneous lesion for accelerating the wound healing process is illustrated in **Figure 2**.

3.4 Recent studies regarding the development of new hydrogel-based dressings for damaged skin regeneration

Hydrogel-based dressings are bioactive dressings, which are extensively used to cure different etiologies wounds because they furnish an optimum pH, suitable exchange of gases, proper regulation of temperature, and adequate local moisture, accelerating the fibroblasts' proliferation and angiogenesis [88]. These dressings present biomimetic characteristics, which make them suitable vehicles for sustained release of various bioactive agents, such as plants extracts, growth factors, nucleotides, inorganic compounds, and analgesic, anti-inflammatory, anesthetic, or antimicrobial active substances, ideal for scaffolds that target the fundamental structures involved in the healing process of the injured skin. Therefore, hydrogel-based dressings can reduce, prevent, and treat the tissue maceration, pain, inflammation, and infection that usually accompany a skin lesion [87]. Recent studies regarding the development of new hydrogel dressings based on different polymers composition and bioactive agents for tissue regeneration are summarized in **Table 1**.

4. Conclusions

Cutaneous lesions care leads to a vast socioeconomic burden, with a huge impact on the patient's quality of life. Thus, this chapter presents a brief approach of hydrogels, which are the most outstanding competitors for the development of new wound dressings from all five classes of modern (advanced) dressings. Hydrogels have attracted the attention of researchers due to their particular 3D structure similar to the extracellular matrix, which has a high capacity to absorb large amounts of water and biological fluids, and which can also retain in their network external microorganisms. These dressings assure optimal moisture at the wound site and a cooling effect, being so comfortable for the patient. Furthermore, hydrogels exhibit a self-healing power, interactive structure, biocompatibility, biodegradability, low cost, nontoxicity, bioadhesion, conductivity, elasticity, softness, swelling behavior, transparency, stimuli-responsive ability, and controlled release of various bioactive agents. As a result of the last feature, this chapter also emphasizes recent studies regarding the development of new wound dressings manufactured using different polymeric supports loaded with various therapeutic agents to stimulate the regeneration of impaired skin tissues.

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Conflict of interest

We, the authors of this paper: Mihaela Violeta Ghica, Cristina-Elena Dinu-Pîrvu, Lăcrămioara Popa, Elena-Emilia Tudoroiu, Diana-Georgiana Ionescu, and Claudia-Maria Benga, declare no conflicts of interests.

Author details

Ghica Mihaela Violeta, Cristina-Elena Dinu-Pîrvu*, Lăcrămioara Popa,
Elena-Emilia Tudoroiu, Diana-Georgiana Ionescu and Claudia-Maria Benga
Faculty of Pharmacy, Carol Davila University of Medicine and Pharmacy Bucharest, Romania

*Address all correspondence to: ecristinaparvu@yahoo.com
and cristina.dinu@umfcd.ro

References

[1] Dabrowska AK, Spano F, Derler S, Adlhart C, Spencer ND, Rossi RM. The relationship between skin function, barrier properties, and body-dependent factors. Skin Research and Technology. 2018;**24**:165-174. DOI: 10.1111/srt.12424

[2] Benson HAE. Skin structure, function, and permeation. In: Benson HAE, Watkinson AC, editors. Topical and Transdermal Drug Delivery: Principles and Practice. 1st ed. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2012. pp. 3-23

[3] Hanel A, Carlberg C. Skin colour and vitamin D: An update. Experimental Dermatology. 2020;**29**:864-875. DOI: 10.1111/exd.14142

[4] Honari G. Skin structure and function. In: Sensitive Skin Syndrome. CRC Press; 2017. pp. 16-22

[5] Zimmerman A, Bai L, Ginty David D. The gentle touch receptors of mammalian skin. Science. 2014;**346**:950-954. DOI: 10.1126/science.1254229

[6] Zaidi Z, Lanigan SW. Skin: Structure and function. In: Dermatology in Clinical Practice. Springer; 2010. pp. 1-15

[7] McGrath JA, Uitto J. Structure and function of the skin. In: Rook's Textbook of Dermatology. 9th ed; 2016. pp. 1-52

[8] Ng KW, Lau WM. Skin deep: The basics of human skin structure and drug penetration. In Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement. Springer; 2015. pp. 3-11

[9] Baroni A, Buommino E, De Gregorio V, Ruocco E, Ruocco V, Wolf R. Structure and function of the epidermis related to barrier properties. Clinics in Dermatology. 2012;**30**:257-262. DOI: 10.1016/j.clindermatol.2011.08.007

[10] Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. New England Journal of Medicine. 2013;**369**:954-964. DOI: 10.1056/NEJMra1203528

[11] Hwa C, Bauer EA, Cohen DE. Skin biology. Dermatologic Therapy. 2011;**24**:464-470. DOI: 10.1111/j.1529-8019.2012.01460.x

[12] Pereira RF, Bartolo PJ. Traditional therapies for skin wound healing. Advances in Wound Care. 2016;**5**:208-229

[13] Martinengo L, Olsson M, Bajpai R, Soljak M, Upton Z, Schmidtchen A, et al. Prevalence of chronic wounds in the general population: Systematic review and meta-analysis of observational studies. Annals of Epidemiology. 2019;**29**:8-15. DOI: 10.1016/j.annepidem.2018.10.005

[14] Kim HS, Sun X, Lee J-H, Kim H-W, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. Advanced Drug Delivery Reviews. 2019;**146**:209-239. DOI: 10.1016/j.addr.2018.12.014

[15] Sen CK. Human wounds and its burden: An updated compendium of estimates. Advances in Wound Care. 2019;**8**:39-48. DOI: 10.1089/wound.2019.0946

[16] Sen CK. Human wound and its burden: Updated 2020 compendium of estimates. Advances in Wound Care. 2021;**10**:281-292. DOI: 10.1089/wound.2021.0026

[17] Järbrink K, Ni G, Sönnergren H, Schmidtchen A, Pang C, Bajpai R, et al. Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. Systematic Reviews. 2016;**5**:152. DOI: 10.1186/s13643-016-0329-y

[18] Gupta S, Sagar S, Maheshwari G, Kisaka T, Tripathi S. Chronic wounds: Magnitude, socioeconomic burden and consequences. Wounds Asia. 2021;**4**: 8-14

[19] Woo K. Wound-related pain: Anxiety, stress and wound healing. Wounds UK. 2010;**6**:92-98

[20] Ahn CS, Maitz PKM. The true cost of burn. Burns. 2012;**38**:967-974. DOI: 10.1016/j.burns.2012.05.016

[21] Weller CD, Team V, Sussman G. First-line interactive wound dressing update: A comprehensive review of the evidence. Frontiers in Pharmacology. 2020;**11**:115. DOI: 10.3389/fphar.2020.00155

[22] Brumberg V, Astrelina T, Malivanova T, Samoilov A. Modern wound dressings: Hydrogel dressings. Biomedicines. 2021;**9**:1235. DOI: 10.3390/biomedicines9091235

[23] Aljghami ME, Saboor S, Amini-Nik S. Emerging innovative wound dressings. Annals of Biomedical Engineering. 2019;**47**:659-675. DOI: 10.1007/s10439-018-02186-w

[24] Zhang M, Zhao X. Alginate hydrogel dressings for advanced wound management. International Journal of Biological Macromolecules. 2020;**162**:1414-1428. DOI: 10.1016/j.ijbiomac.2020.07.311

[25] Borda LJ, Macquhae FE, Kirsner RS. Wound dressings: A comprehensive review. Current Dermatology Reports. 2016;**5**:287-297. DOI: 10.1007/s13671-016-0162-5

[26] Kamoun EA, Kenawy E-RS, Chen X. A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. Journal of Advanced Research. 2017;**8**:217-233. DOI: 10.1016/j.jare.2017.01.005

[27] Moeini A, Pedram P, Makvandi P, Malinconico M, Gomez d'Ayala G. Wound healing and antimicrobial effect of active secondary metabolites in chitosan-based wound dressings: A review. Carbohydrate Polymers. 2020;**233**:115839. DOI: 10.1016/j.carbpol.2020.115839

[28] An Y-H, Yu SJ, Kim IS, Kim S-H, Moon J-M, Kim SL, et al. Hydrogel functionalized Janus membrane for skin regeneration. Advanced Healthcare Materials. 2017;**6**:1600795. DOI: 10.1002/adhm.201600795

[29] Simões D, Miguel SP, Ribeiro MP, Coutinho P, Mendonça AG, Correia IJ. Recent advances on antimicrobial wound dressing: A review. European Journal of Pharmaceutics and Biopharmaceutics. 2018;**127**:130-141. DOI: 10.1016/j.ejpb.2018.02.022

[30] Boateng J, Catanzano O. Advanced therapeutic dressings for effective wound healing—A review. Journal of Pharmaceutical Sciences. 2015;**104**:3653-3680. DOI: 10.1002/jps.24610

[31] Leite MN, Leite SN, Caetano GF, Andrade TAMd, Fronza M, Frade MAC. Healing effects of natural latex serum 1% from Hevea brasiliensis in an experimental skin abrasion wound model. Anais Brasileiros de Dermatologia. 2020;**95**:418-427. DOI: 10.1016/j.abd.2019.12.003

[32] Sakai G, Suzuki T, Hishikawa T, Shirai Y, Kurozumi T, Shindo M. Primary reattachment of avulsed skin flaps with negative pressure wound therapy in degloving injuries of the lower extremity. Injury. 2017;**48**:137-141. DOI: 10.1016/j.injury.2016.10.026

[33] Yang Y, Zhao X, Yu J, Chen X, Wang R, Zhang M, et al. Bioactive skin-mimicking hydrogel band-aids for diabetic wound healing and infectious skin incision treatment. Bioactive Materials. 2021;**6**:3962-3975. DOI: 10.1016/j.bioactmat.2021.04.007

[34] Agrawal P, Soni S, Mittal G, Bhatnagar A. Role of polymeric biomaterials as wound healing agents. The International Journal of Lower Extremity Wounds. 2014;**13**:180-190. DOI: 10.1177/1534734614544523

[35] Prasathkumar M, Sadhasivam S. Chitosan/hyaluronic acid/alginate and an assorted polymers loaded with honey, plant, and marine compounds for progressive wound healing—Know-how. International Journal of Biological Macromolecules. 2021;**186**:656-685. DOI: 10.1016/j.ijbiomac.2021.07.067

[36] Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: A review. Journal of Pharmaceutical Sciences. 2008;**97**:2892-2923. DOI: 10.1002/jps.21210

[37] Understanding traumatic wounds. Nursing Made Incredibly Easy. 2008;**6**(7):9-10. DOI: 10.1097/01.NME.0000316721.61614.da

[38] Chen X, Zhai D, Wang B, Hao S, Song J, Peng Z. Hair keratin promotes wound healing in rats with combined radiation-wound injury. Journal of Materials Science. Materials in Medicine. 2020;**31**:28. DOI: 10.1007/s10856-020-06365-x

[39] Leau S-A, Marin Ş, CoarĂ G, Albu L, Constantinescu RR, Albu Kaya M, et al. Study of Wound-Dressing Materials Based on Collagen, Sodium Carboxymethylcellulose and Silver Nanoparticles Used for Their Antibacterial Activity in Burn Injuries. 2018. pp. 123-128

[40] Sandri G, Bonferoni MC, D'Autilia F, Rossi S, Ferrari F, Grisoli P, et al. Wound dressings based on silver sulfadiazine solid lipid nanoparticles for tissue repairing. European Journal of Pharmaceutics and Biopharmaceutics. 2013;**84**:84-90. DOI: 10.1016/j.ejpb.2012.11.022

[41] Monavarian M, Kader S, Moeinzadeh S, Jabbari E. Regenerative scar-free skin wound healing. Tissue Engineering Part B: Reviews. 2019;**25**:294-311. DOI: 10.1089/ten.teb.2018.0350

[42] O'Brien CJCFP. Malignant wounds: managing odour. Canadian Family Physician. 2012;**58**:272-274

[43] Merzoug-Larabi M, Spasojevic C, Eymard M, Hugonin C, Auclair C, Karam M. Protein kinase C inhibitor Gö6976 but not Gö6983 induces the reversion of E- to N-cadherin switch and metastatic phenotype in melanoma: Identification of the role of protein kinase D1. BMC Cancer. 2017;**17**:12. DOI: 10.1186/s12885-016-3007-5

[44] McLafferty E, Hendry C, Farley A. The integumentary system: Anatomy, physiology and function of skin. Nursing Standard (through 2013). 2012;**27**:35-42

[45] Nasiri E, Mollaei A, Birami M, Lotfi M, Rafiei MH. The

risk of surgery-related pressure ulcer in diabetics: A systematic review and meta-analysis. Annals of Medicine and Surgery. 2021;**65**:102336. DOI: 10.1016/j.amsu.2021.102336

[46] McInnes E, Jammali-Blasi A, Bell-Syer SE, Dumville JC, Middleton V, Cullum N. Support surfaces for pressure ulcer prevention. Cochrane Database of Systematic Reviews. 2015:CD001735. DOI: 10.1002/14651858.CD001735.pub5

[47] Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World Journal of Diabetes. 2015;**6**:37-53. DOI: 10.4239/wjd.v6.i1.37

[48] Rezvanian M, Tan CK, Ng SF. Simvastatin-loaded lyophilized wafers as a potential dressing for chronic wounds. Drug Development and Industrial Pharmacy. 2016;**42**:2055-2062. DOI: 10.1080/03639045.2016.1195400

[49] Valente S, Ciavarella C, Pasanisi E, Ricci F, Stella A, Pasquinelli G. Hepatocyte growth factor effects on mesenchymal stem cells derived from human arteries: A novel strategy to accelerate vascular ulcer wound healing. Stem Cells International. 2016;**2016**:3232859. DOI: 10.1155/2016/3232859

[50] Brown MJ, Curry TB, Hyder JA, Berbari EF, Truty MJ, Schroeder DR, et al. Intraoperative hypothermia and surgical site infections in patients with class I/clean wounds: A case-control study. Journal of the American College of Surgeons. 2017;**224**:160-171. DOI: 10.1016/j.jamcollsurg.2016.10.050

[51] Gorvetzian JW, Epler KE, Schrader S, Romero JM, Schrader R, Greenbaum A, et al. Operating room staff and surgeon documentation curriculum improves wound classification accuracy. Heliyon. 2018;**4**:e00728. DOI: 10.1016/j.heliyon.2018.e00728

[52] Dayama A, Fontecha CA, Foroutan S, Lu J, Kumar S, Matolo NM. Comparison of surgical incision complete closure versus leaving skin open in wound class IV in emergent colon surgery. The American Journal of Surgery. 2018;**216**:240-244. DOI: 10.1016/j.amjsurg.2017.05.010

[53] Yamamoto T, Yamamoto N. Mango cut incision for pressure ulcer necrotic tissue clearance: An easier and safer method to facilitate chemical debridement in severely-comorbid patients. Wound Medicine. 2017;**18**:43-46. DOI: 10.1016/j.wndm.2017.07.003

[54] Chong HC, Fong KK, Hayati F. Skin ulceration as a complication from unexpected extravasation injury: A case report. Annals of Medicine and Surgery. 2021;**64**:102267. DOI: 10.1016/j.amsu.2021.102267

[55] Wang H, Gu Y, Huang L, Zeng Z, Hu X, Wang X, et al. Effectiveness of fire needle combining with moist healing dressing to promote the growth of granulation tissue in chronic wounds: A case report. International Journal of Nursing Sciences. 2020;**7**:386-390. DOI: 10.1016/j.ijnss.2020.05.008

[56] Waehle V, Ungricht R, Hoppe PS, Betschinger J. The tumor suppressor WT1 drives progenitor cell progression and epithelialization to prevent Wilms tumorigenesis in human kidney organoids. Stem Cell Reports. 2021;**16**:2107-2117. DOI: 10.1016/j.stemcr.2021.07.023

[57] Bue M, Bergholt NL, Jensen LK, Jensen HE, Søballe K, Stilling M, et al.

Inflammatory proteins in infected bone tissue—An explorative porcine study. Bone Reports. 2020;**13**:100292. DOI: 10.1016/j.bonr.2020.100292

[58] Lukish J, Stewart D, Goldstein S, Garcia A, Pryor H, Rhee D, et al. Microdeformational wound therapy: A novel option to salvage complex wounds associated with the Nuss procedure. Journal of Pediatric Surgery. 2019;**54**:1500-1504. DOI: 10.1016/j.jpedsurg.2019.03.006

[59] Yang Y-H, Jeng S-F, Hsieh C-H, Feng G-M, Chen CC. Vacuum-assisted closure for complicated wounds in head and neck region after reconstruction. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2013;**66**:e209-e216. DOI: 10.1016/j.bjps.2013.03.006

[60] Loan F, Cassidy S, Marsh C, Simcock J. Keratin-based products for effective wound care management in superficial and partial thickness burns injuries. Burns. 2016;**42**:541-547. DOI: 10.1016/j.burns.2015.10.024

[61] Praveen S, Rohaizak M. Local antibiotics are equivalent to intravenous antibiotics in the prevention of superficial wound infection in inguinal hernioplasty. Asian Journal of Surgery. 2009;**32**:59-63. DOI: 10.1016/S1015-9584(09)60011-7

[62] Jabeen S, Clough ECS, Thomlinson AM, Chadwick SL, Ferguson MWJ, Shah M. Partial thickness wound: Does mechanism of injury influence healing? Burns. 2019;**45**:531-542. DOI: 10.1016/j.burns.2018.08.010

[63] Frew Q, Rennekampff H-O, Dziewulski P, Moiemen N, Zahn T, Hartmann B. Betulin wound gel accelerated healing of superficial partial thickness burns: Results of a randomized, intra-individually controlled, phase III trial with 12-months follow-up. Burns. 2019;**45**:876-890. DOI: 10.1016/j.burns.2018.10.019

[64] Zandi N, Dolatyar B, Lotfi R, Shallageh Y, Shokrgozar MA, Tamjid E, et al. Biomimetic nanoengineered scaffold for enhanced full-thickness cutaneous wound healing. Acta Biomaterialia. 2021;**124**:191-204. DOI: 10.1016/j.actbio.2021.01.029

[65] He Y, Zhao W, Dong Z, Ji Y, Li M, Hao Y, et al. A biodegradable antibacterial alginate/carboxymethyl chitosan/Kangfuxin sponges for promoting blood coagulation and full-thickness wound healing. International Journal of Biological Macromolecules. 2021;**167**:182-192. DOI: 10.1016/j.ijbiomac.2020.11.168

[66] Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: A cellular perspective. Physiological Reviews. 2018;**99**:665-706. DOI: 10.1152/physrev.00067.2017

[67] Yazarlu O, Iranshahi M, Kashani HRK, Reshadat S, Habtemariam S, Iranshahy M, et al. Perspective on the application of medicinal plants and natural products in wound healing: A mechanistic review. Pharmacological Research. 2021;**174**:105841. DOI: 10.1016/j.phrs.2021.105841

[68] Tatara AM, Kontoyiannis DP, Mikos AG. Drug delivery and tissue engineering to promote wound healing in the immunocompromised host: Current challenges and future directions. Advanced Drug Delivery Reviews. 2018;**129**:319-329. DOI: 10.1016/j.addr.2017.12.001

[69] Pulido T, Velarde MC, Alimirah F. The senescence-associated secretory

phenotype: Fueling a wound that never heals. Mechanisms of Ageing and Development. 2021;**199**:111561. DOI: 10.1016/j.mad.2021.111561

[70] Thomas DC, Tsu CL, Nain RA, Arsat N, Fun SS, Lah SN, et al. The role of debridement in wound bed preparation in chronic wound: A narrative review. Annals of Medicine and Surgery. 2021;**102876**. DOI: 10.1016/j.amsu.2021.102876

[71] Falcone M, De Angelis B, Pea F, Scalise A, Stefani S, Tasinato R, et al. Challenges in the management of chronic wound infections. Journal of Global Antimicrobial Resistance. 2021;**26**:140-147. DOI: 10.1016/j.jgar.2021.05.010

[72] Pawar HV, Tetteh J, Boateng JS. Preparation, optimisation and characterisation of novel wound healing film dressings loaded with streptomycin and diclofenac. Colloids and Surfaces. B, Biointerfaces. 2013;**102**:102-110. DOI: 10.1016/j.colsurfb.2012.08.014

[73] Op't Veld RC, Walboomers XF, Jansen JA, Wagener F. Design considerations for Hydrogel wound dressings: Strategic and molecular advances. Tissue Engineering—Part B: Reviews. 2020;**26**:230-248. DOI: 10.1089/ten.teb.2019.0281

[74] Gupta A, Kowalczuk M, Heaselgrave W, Britland ST, Martin C, Radecka I. The production and application of hydrogels for wound management: A review. European Polymer Journal. 2019;**111**:134-151. DOI: 10.1016/j.eurpolymj.2018.12.019

[75] Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research. 2015;**6**:105-121. DOI: 10.1016/j.jare.2013.07.006

[76] Holback H, Yeo Y, Park K. 1—Hydrogel swelling behavior and its biomedical applications. In: Biomedical Hydrogels, Rimmer S. Ed. Woodhead Publishing; 2011. pp. 3-24

[77] Aswathy SH, Narendrakumar U, Manjubala I. Commercial hydrogels for biomedical applications. Heliyon. 2020;**6**:e03719. DOI: 10.1016/j.heliyon.2020.e03719

[78] Vasile C, Pamfil D, Stoleru E, Baican M. New developments in medical applications of hybrid hydrogels containing natural polymers. Molecules. 2020;**25**. DOI: 10.3390/molecules25071539

[79] Elsayed MM. Hydrogel preparation technologies: Relevance kinetics, thermodynamics and scaling up aspects. Journal of Polymers and the Environment. 2019;**27**:871-891. DOI: 10.1007/s10924-019-01376-4

[80] Ullah F, Othman MBH, Javed F, Ahmad Z, Akil HM. Classification, processing and application of hydrogels: A review. Materials Science and Engineering: C. 2015;**57**:414-433. DOI: 10.1016/j.msec.2015.07.053

[81] Varaprasad K, Raghavendra GM, Jayaramudu T, Yallapu MM, Sadiku R. A mini review on hydrogels classification and recent developments in miscellaneous applications. Materials Science and Engineering: C. 2017;**79**:958-971. DOI: 10.1016/j.msec.2017.05.096

[82] Khan S, Ullah A, Ullah K, Rehman N-U. Insight into hydrogels. Designed Monomers and Polymers. 2016;**19**:456-478. DOI: 10.1080/15685551.2016.1169380

[83] Liang Y, He J, Guo B. Functional hydrogels as wound dressing to enhance wound healing. ACS Nano. 2021;**15**:12687-12722. DOI: 10.1021/acsnano.1c04206

[84] Koehler J, Brandl FP, Goepferich AM. Hydrogel wound dressings for bioactive treatment of acute and chronic wounds. European Polymer Journal. 2018;**100**:1-11. DOI: 10.1016/j.eurpolymj.2017.12.046

[85] Namazi H, Rakhshaei R, Hamishehkar H, Kafil HS. Antibiotic loaded carboxymethylcellulose/MCM-41 nanocomposite hydrogel films as potential wound dressing. International Journal of Biological Macromolecules. 2016;**85**:327-334. DOI: 10.1016/j.ijbiomac.2015.12.076

[86] Wang ZC, Wang YX, Peng XY, He YL, Wei L, Su WH, et al. Photocatalytic antibacterial agent incorporated double-network hydrogel for wound healing. Colloids and Surfaces B: Biointerfaces. 2019;**180**:237-244. DOI: 10.1016/j.colsurfb.2019.04.043

[87] Kus KJB, Ruiz ES. Wound dressings—A practical review. Current Dermatology Reports. 2020;**9**:298-308. DOI: 10.1007/s13671-020-00319-w

[88] Zelga PJ, Gornicz MM, Gluszkiewicz JM, Piasecka-Zelga J. Outcomes of acute dermal irritation and sensitisation tests on active dressings for chronic wounds: A comparative study. Journal of Wound Care. 2016;**25**:722-729. DOI: 10.12968/jowc.2016.25.12.722

[89] Wang Y, Pang XL, Luo J, Wen Q, Wu ZX, Ding QX, et al. Naproxen nanoparticle-loaded thermosensitive chitosan hydrogel for prevention of postoperative adhesions. ACS Biomaterials Science & Engineering. 2019;**5**:1580-1588. DOI: 10.1021/acsbiomaterials.8b01562

[90] Xu QZ, Wang YY, Chen TJ, Lao CW, Gao HK, Wei R, et al. A distinctive nanocomposite hydrogel integrated platform for the healing of wound after the resection of melanoma. Materialia. 2020;**14**:14. DOI: 10.1016/j.mtla.2020.100931

[91] Oh KS, Hwang C, Lee HY, Song JS, Park HJ, Lee CK, et al. Preclinical studies of ropivacaine extended-release from a temperature responsive hydrogel for prolonged relief of pain at the surgical wound. International Journal of Pharmaceutics. 2019;**558**:225-230. DOI: 10.1016/j.ijpharm.2019.01.011

[92] Kulshrestha S, Chawla R, Singh S, Yadav P, Sharma N, Goel R, et al. Protection of sildenafil citrate hydrogel against radiation-induced skin wounds. Burns. 2020;**46**:1157-1169. DOI: 10.1016/j.burns.2019.11.020

[93] Zhang J, Zhu Y, Zhang Y, Lin W, Ke J, Liu J, et al. A balanced charged hydrogel with anti-biofouling and antioxidant properties for treatment of irradiation-induced skin injury. Materials Science and Engineering: C. 2021;**131**:112538. DOI: 10.1016/j.msec.2021.112538

[94] Nuutila K, Grolman J, Yang L, Broomhead M, Lipsitz S, Onderdonk A, et al. Immediate treatment of burn wounds with high concentrations of topical antibiotics in an alginate Hydrogel using a platform wound device. Advances in Wound Care. 2020;**9**:48-60. DOI: 10.1089/wound.2019.1018

[95] Mu B, Wang RF, Gao J, Li ZY, Li X. Nano gold incorporated intoAerva javanicachitosan hydrogels disrupting agents against infections of burn wound. Materials and Technologies. 2021;**36**:783-792. DOI: 10.1080/10667857.2020.1794331

[96] Roy DC, Tomblyn S, Isaac KM, Kowalczewski CJ, Burmeister DM, Burnett LR, et al. Ciprofloxacin-loaded keratin hydrogels reduce infection and support healing in a porcine partial-thickness thermal burn. Wound Repair

and Regeneration. 2016;**24**:657-668. DOI: 10.1111/wrr.12449

[97] Qiu YM, Sun XX, Lin XL, Yi WY, Jiang JY. An injectable metal nanoparticle containing cellulose derivative-based hydrogels: Evaluation of antibacterial and in vitro-vivo wound healing activity in children with burn injuries. International Wound Journal. 2022;**19**:666-678. DOI: 10.1111/iwj.13664

[98] Heimbuck AM, Priddy-Arrington TR, Padgett ML, Llamas CB, Barnett HH, Bunnell BA, et al. Development of responsive chitosan-genipin hydrogels for the treatment of wounds. ACS Applied Bio Materials. 2019;**2**:2879-2888. DOI: 10.1021/acsabm.9b00266

[99] Choipang C, Chuysinuan P, Suwantong O, Ekabutr P, Supaphol P. Hydrogel wound dressings loaded with PLGA/ciprofloxacin hydrochloride nanoparticles for use on pressure ulcers. Journal of Drug Delivery Science and Technology. 2018;**47**:106-114. DOI: 10.1016/j.jddst.2018.06.025

[100] Lu K, Li KK, Zhang M, Fang ZX, Wu PP, Feng LB, et al. Adipose-derived stem cells (ADSCs) and platelet-rich plasma (PRP) loaded gelatin/silk fibroin hydrogels for improving healing in a murine pressure ulcer model. Chemical Engineering Journal. 2021;**424**:12. DOI: 10.1016/j.cej.2021.130429

[101] Stefanov I, Perez-Rafael S, Hoyo J, Cailloux J, Perez OOS, Hinojosa-Caballero D, et al. Multifunctional enzymatically generated Hydrogels for chronic wound application. Biomacromolecules. 2017;**18**:1544-1555. DOI: 10.1021/acs.biomac.7b00111

[102] Gilmartin DJ, Soon A, Thrasivoulou C, Phillips ARJ, Jayasinghe SN, Becker DL. Sustained release of Cx43 antisense oligodeoxynucleotides from coated collagen scaffolds promotes wound healing. Advanced Healthcare Materials. 2016;**5**:1786-1799. DOI: 10.1002/adhm.201600175

[103] Morgado PI, Miguel SP, Correia IJ, Aguiar-Ricardo A. Ibuprofen loaded PVA/chitosan membranes: A highly efficient strategy towards an improved skin wound healing. Carbohydrate Polymers. 2017;**159**:136-145. DOI: 10.1016/j.carbpol.2016.12.029

[104] Shin DY, Park JU, Choi MH, Kim S, Kim HE, Jeong SH. Polydeoxyribonucleotide-delivering therapeutic hydrogel for diabetic wound healing. Scientific Reports. 2020;**10**:14. DOI: 10.1038/s41598-020-74004-0

[105] Chen YH, Rao ZF, Liu YJ, Liu XS, Liu YF, Xu LJ, et al. Multifunctional injectable hydrogel loaded with cerium-containing bioactive glass nanoparticles for diabetic wound healing. Biomolecules. 2021;**11**:17. DOI: 10.3390/biom11050702

[106] El-Salamouni NS, Gowayed MA, Seiffein NL, Abdel-Moneim RA, Kamel MA, Labib GS. Valsartan solid lipid nanoparticles integrated hydrogel: A challenging repurposed use in the treatment of diabetic foot ulcer, in-vitro/in-vivo experimental study. International Journal of Pharmaceutics. 2021;**592**:19. DOI: 10.1016/j.ijpharm.2020.120091

[107] Li ZH, Zhao Y, Liu H, Ren M, Wang ZH, Wang XG, et al. pH-responsive hydrogel loaded with insulin as a bioactive dressing for enhancing diabetic wound healing. Materials and Design. 2021;**210**:12. DOI: 10.1016/j.matdes.2021.110104

[108] Wang T, Li YR, Cornel EJ, Li C, Du JZ. Combined antioxidant-antibiotic

treatment for effectively healing infected diabetic wounds based on polymer vesicles. ACS Nano. 2021;**15**:9027-9038. DOI: 10.1021/acsnano.1c02102

[109] Rapalli VK, Sharma S, Roy A, Alexander A, Singhvi G. Solid lipid nanocarriers embedded hydrogel for topical delivery of apremilast: In-vitro, ex-vivo, dermatopharmacokinetic and anti-psoriatic evaluation. Journal of Drug Delivery Science and Technology. 2021;**63**:17. DOI: 10.1016/j.jddst.2021.102442

[110] Bernardes M, Agostini SBN, Pereira GR, da Silva LP, da Silva JBD, Bruschi ML, et al. Preclinical study of methotrexate-based hydrogels versus surfactant based liquid crystal systems on psoriasis treatment. European Journal of Pharmaceutical Sciences. 2021;**165**:12. DOI: 10.1016/j.ejps.2021.105956

[111] Kumar S, Prasad M, Rao R. Topical delivery of clobetasol propionate loaded nanosponge hydrogel for effective treatment of psoriasis: Formulation, physicochemical characterization, antipsoriatic potential and biochemical estimation. Materials Science & Engineering C-Materials for Biological Applications. 2021;**119**:19. DOI: 10.1016/j.msec.2020.111605

[112] Li Q, Li FM, Qi XX, Wei FQ, Chen HX, Wang T. Pluronic (R) F127 stabilized reduced graphene oxide hydrogel for the treatment of psoriasis: In vitro and in vivo studies. Colloids and Surfaces B: Biointerfaces. 2020;**195**:6. DOI: 10.1016/j.colsurfb.2020.111246

[113] Fernandez-Romero AM, Maestrelli F, Garcia-Gil S, Talero E, Mura P, Rabasco AM, et al. Preparation, characterization and evaluation of the anti-inflammatory activity of epichlorohydrin-beta-cyclodextrin/curcumin binary systems embedded in a Pluronic(R)/hyaluronate Hydrogel. International Journal of Molecular Sciences. 2021;**22**:26. DOI: 10.3390/ijms222413566