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Research Article

HYDROGEL AN NOVEL APPROACH FOR WOUND DRESSINGS: A REVIEW

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ABTRACT

Skin is the largest organ of the human body, protecting it against the external environment. Despite high self-regeneration potential, severe skin defects will not heal spontaneously and need to be covered by skin substitutes. Tremendous progress has been made in the field of skin tissue engineering, in recent years, to develop new skin substitutes. This review has mainly been focused on achieving the specifications of an ideal wound dressing. This chapter discusses the use of hydrogels, both natural and synthetic, that can be used for wound healing applications. Owing to the merits of high porosity, good biocompatibility, tunable physicochemical properties, and being beneficial for wound healing, hydrogels with excellent performance have drawn intensive attention and numerous novel effective hydrogel dressings have been widely developed. In this Review, after introducing some commonly used strategies for the synthesis of hydrogels, the most recent progress on polymer-based hydrogels as wound dressings is discussed. Finally, challenges and future perspectives about the development of hydrogels for wound dressings are outlined.

Keywords: Hydrogels, wound dressings, wound classification, and wound healing.

INTRODUCTION

Wounds represent a "silent epidemic" amongst the world population, with a terrific social and economic impact, affecting the quality of life of hundreds of thousands of people. While acute wound management in a healthful patient is rather extra approachable, patients with chronic wounds can signify a actual challenge in terms of wound assessment and management. An evaluation of Medicare archives confirmed that ~8.2 million people suffered from acute or persistent wounds, with charges of up to $96.8 billion.[1] In Europe, ~2 million humans go through from chronic wounds, whilst in the United States ~2% of the total population are estimated to be affected via chronic wounds.[1,2] Doctors and nurses caring for sufferers with wounds can have a massive affect at a couple of levels, social, financial and personal, so it is important that the constantly improve. Knowledge about pores and skin physiology and function, as properly as wound healing mechanisms, can allow healthcare staff to better care for wound suffering patients. This primary information will permit the patient to be correctly and efficiently evaluated so that the excellent cure plan can be chosen for him. The final aim is to have the high-quality tools for wound management that will enable clinical team of workers to diagnose, make a prognosis and a personalised therapy plan. Wound restoration is a dynamic process and the potential to adapt the cure plan to changes in the wound site or the patient's surroundings will have a essential influence on patient's recovery and quality of life. Because of these, significant research have been carried out on the topic of wound healing approaches and wound management devices. Hydrogel wound dressings and creams can enhance healing and have a beneficial have an impact on on the ultimate outcome. Smart hydrogels allow real-time wound monitoring and can be used as a conveyance vehicle for bioactive compounds.[3,4]

SKIN ANATOMY

The pores and skin is the biggest organ in the human body, being accountable for about 16% of whole physique weight. The two most important structural layers that structure the skin are the dermis and the dermis, joined by way of the basement membrane (Figure 1). Below these layers, there is the subcutaneous tissue—the hypodermis, with the adipose tissue. The epidermis is divided into five layers: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale. Stratum lucidum is solely determined in thick skin. In the classical literature, a sixth layer is also described, derived from the non-stop exfoliation of the stratum corneum, the desquamation layer. The dermis consists of two layers: papillary dermis (superficial) and reticular dermis (deep). Regarding the embryonic origin, the epidermis is derived from the ectoderm and is colonized via keratinocytes, melanocytes and Merkel cells originating in the neural crest and Langerhans cells originating in the bone marrow. The dermis and the hypodermis are derived from the mesoderm. It consists of fibroblasts, collagen and elastic fibres, proteoglycans and glycosaminoglycans, free and encapsulated nerve endings, Schwann cells, endothelial cells geared up in the structure of vessels, pericytes, mast cells, tissue macrophages and other cells of the immune system. Skin traits and properties (eg thickness, elasticity) differ relying on many parameters (eg age, sex, anatomical location).[5–7]

At the stage of the dermis, which is a dense irregular connective tissue, there is an plentiful extracellular matrix, consisting of specialised proteins and carbohydrates. The papillary layer, which begins at the degree of the epidermal basement membrane, is in the main populated with fibroblasts and the reticular layer consists of mostly thick collagen fibres.[8] The dermis offers metabolic and mechanical support for the epidermis due to its specific structure that approves it to hold its integrity even in case of exposure to excessive mechanical stress. If injuries occur, the dermis does now not regenerate, at this level a repair process takes place. Under the dermis, there is the hypodermis which is a kind of connective tissue in the main consisting of adipocytes. This layer separates the dermis from other structures such as fascia, muscle mass or bone. In the case of a pores and skin wound, the hypodermis does now not regenerate, being changed by way of scar tissue rich in collagen.[9–14]

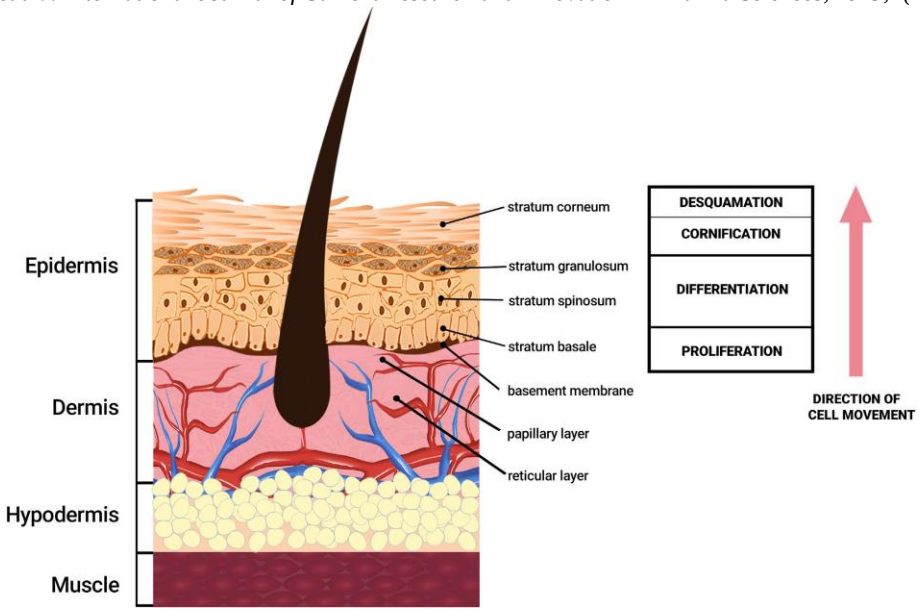


Figure 1: Basic anatomy of skin.

SKIN FUNCTIONS

Skin features (Figure 2) are reflected by using its structural characteristics. First of all, it is a protecting barrier towards the detrimental environmental factors, with an important position in keeping the body's homeostasis. The tight intercellular junctions and the stratum corneum structure the mechanical barrier. The microbiome, the chemical and the immunological barriers additionally take part in the fulfilment of the barrier function. Many proteins such as cystatin, desmoplakin and filaggrin make a contribution to the achievement of this role, whilst the hydrophobic layer of lipids prevents water loss.[16,17] The keratinocytes from the spinous layer produce keratohyalin granules and lamellar our bodies containing a combination of glycosphingolipids, phospholipids and ceramides, these lipids are released by way of the lamellar our bodies into the extracellular space and strengthen the barrier feature of the skin.[18] Immune feature is due to both cellular immunity (Langerhans cells or dendritic epidermal T cells) and humoral immunity. In addition, antimicrobial peptides that are produced by means of keratinocytes and by way of the cells of the immune system are involved in the technique of inflammation and wound recovery and are advantageous on a broad range of pathogens such as bacteria, fungi or viruses.[19] By regulating the temperature and the water and electrolytes losses, the pores and skin contributes to keeping homeostasis. Endocrine characteristic consists of diet D production, and exocrine characteristic is carried out through the sebaceous and sweat glands.[20–22]

The barrier characteristic of the pores and skin is influenced via many factors. For the pores and skin to fulfil this role, it desires to be each structurally and metabolically intact. An essential function in assisting the barrier function of the pores and skin is performed by way of the pH value. At the stage of the stratum corneum, the pH varies relying on the anatomical area, the normal values being between 4 and 5.8, whilst at the stage of the granular layer the pH has greater values. At the stage of the groin, axilla and between the toes, the pH is between 6 and 7.4. Changes in the pH cost outside, the physiological limits can lead to impaired pores and skin barrier function with the aid of altering the microbiome, lipid synthesis and enzymatic activity. In addition, the pH alteration affects the technique of epidermal differentiation and desquamation. The exceptional of intercellular junctions additionally influences the barrier characteristic of the skin. These junctions structure a barrier for molecules of one of a kind sizes however additionally for ions, so that a negative exceptional influences the permeability. The junction's formation and their effectiveness depend

on the presence of sure proteins such as cingulin, claudin or occluding.[23–26]

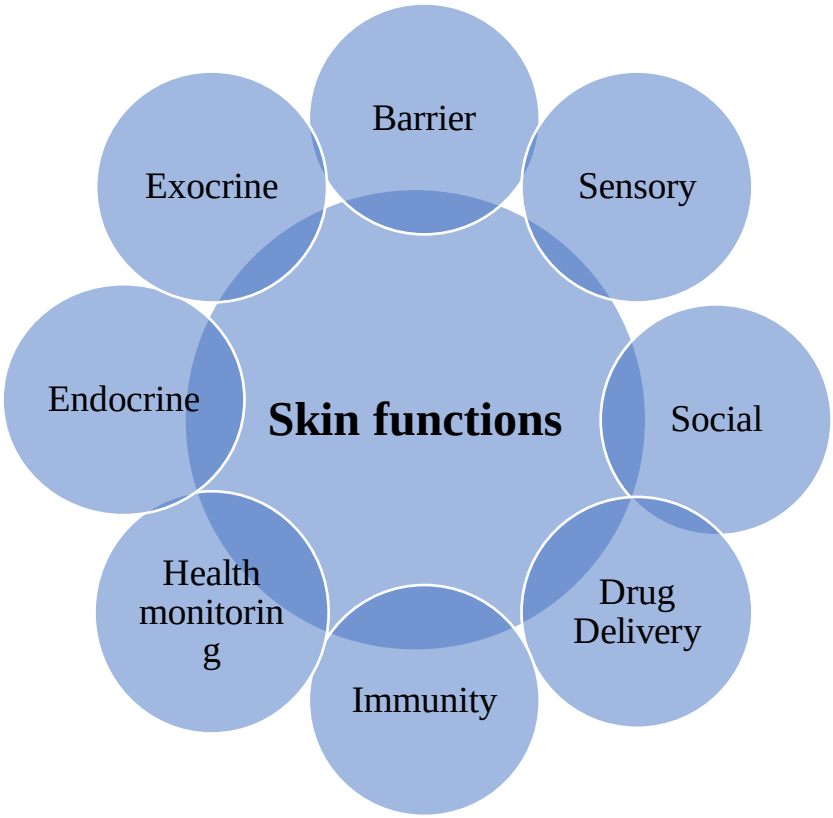


Figure 2: Skin functions. The barrier function is one of the most important functions of the skin, because it maintains the body's homeostasis and protects against pathogens, chemicals, radiation and mechanical damage.

Skin wounds:

The wounds manifest due to disruption of the epithelial layer and the integrity of living tissue.[27] They can be triggered by way of a number of exterior factors, such as burns, surgical procedures, and trauma and internal, such as nearby blood supply disorders. Skin lesions are categorized into two categories: acute, which eventually heals inside a duration of eight to 12 weeks, and chronic, which takes months and, in some cases, years till they heal absolutely.[28,29] There is a direct correlation between cuts with the aid of sharp objects, lacerations prompted by means of firearms, and burns in acute injuries. For example, this ultimate lesion can have an effect on the three layers of the pores and skin.[30–32] First-degree burns have an effect on the epidermis; the 2nd degree affects the epidermis and the dermis; the 0.33 degree impacts all three layers of the pores and skin.[33] However, the healing technique typically takes place, respecting the limits of the size of the wounds and the affected layers.[34,35] On the other hand, continual accidents can manifest due to diabetes, stress ulcers, or perforation in arteries.[36] One of these wounds' most important characteristics is the persistence of dead tissue in the injured region.[37] Furthermore, some elements obstruct this recovery process, ranging from inadequate blood provide in the damaged area to overseas our bodies or infections triggered through microorganisms, main to the look of exudate/pus.[38] As this kind of wound is associated to tissue degradation, the overall performance of chemical and biochemical agents, such as neutrophils, is accentuated 10 to forty instances extra than in acute injuries, main to a deterioration of each hormones and elements of growth, which helps in delaying the recovery technique.[39]

1. **Class 1:** wounds are considered to be clean. They are uninfected, no inflammation is present, and are primarily closed. If the draining of these wounds is necessary, a closed draining method is necessary. Additionally, these wounds do not enter respiratory, alimentary, genital, or urinary tracts.

2. **Class 2:** wounds are considered to be clean-contaminated. These wounds lack unusual contamination. Class 2 wounds enter the respiratory, alimentary, genital, or urinary tracts. However, these wounds have entered these tracts under controlled conditions.
3. **Class 3:** wounds are considered to be contaminated. These are fresh, open wounds that can result from insult to sterile techniques or leakage from the gastrointestinal tract into the wound. Additionally, incisions made that result in acute or lack of purulent inflammation are considered class 3 wounds.
4. **Class 4:** wounds are considered to be dirty-infected. These wounds typically result from improperly cared for traumatic wounds. Class 4 wounds demonstrate devitalized tissue, and they most commonly result from microorganisms present in perforated viscera or the operative field.[40]

Skin Wound Healing

Wound healing is a dynamic and complicated technique that can be divided into 4 subsequent and overlapping phases—homeostasis (blood clotting), inflammation, tissue increase (proliferation), and tissue redesigning (maturation).[42,43] Within the first few minutes after injury, blood platelets begin to stick to one some other and to the wound site. In contact with collagen, platelets alternate into an amorphous shape, ensuing in their activation and aggregation. Further, thrombin begins to be produced and catalyzes the initiation of the coagulation cascade.[44,45] This, in turn, consequences in the activation of fibrin, which types a mesh stopping in addition bleeding.[46] Moreover, platelets have a fundamental function in leukocyte recruitment and the initiation and growth of inflammation.[47] In the inflammatory phase, immune cells (particularly neutrophils and macrophages) are recruited into the wound, the place they phagocyte damaged and dead cells, bacteria, and different pathogens or particles. Moreover, inflammatory cells collectively with platelets release more than a few peptides increase factors, promoting the migration of fibroblasts into the wound site and activating angiogenesis. During the proliferation phase, fibroblasts are in addition influenced to proliferate in the wound area. Further, they reconstitute the dermal tissue elements through formation of granulation tissue and deposition of extracellular matrix proteins, typically collagen. Furthermore, improved angiogenesis induces ingrowth of a new network of blood vessels into the granulation tissue to enhance cell survival by way of offering enough levels of oxygen and nutrients. Afterward, epithelial cells migrate from the wound edges to cover the defect, a technique acknowledged as 'epithelialization'.[48–51]

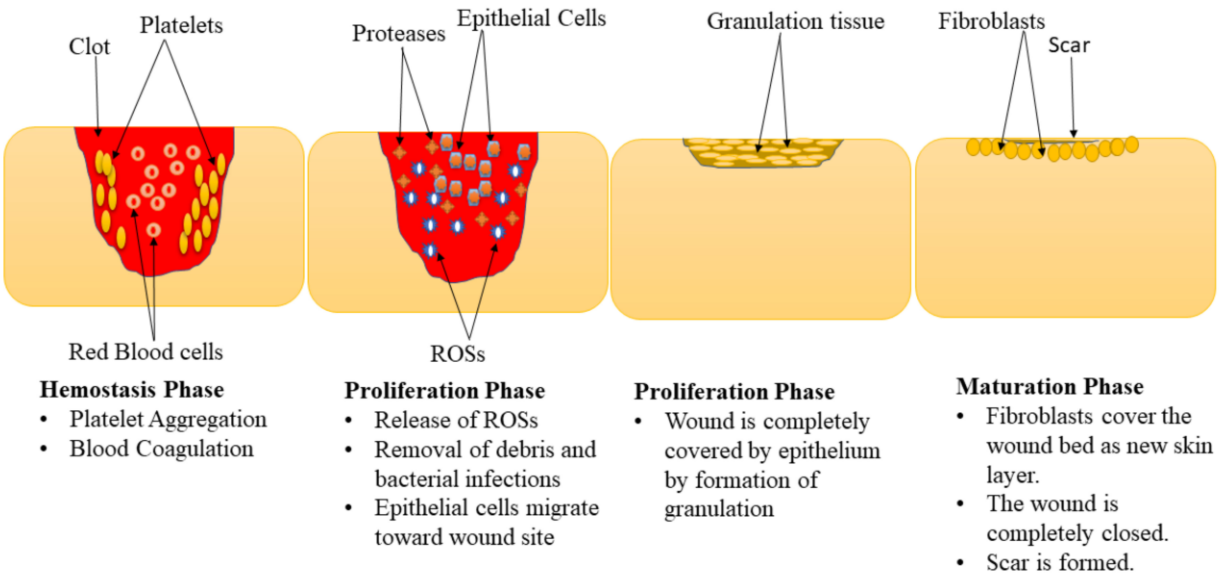


Figure 3: Phases of the wound healing process.

In the proliferation phase, the epithelium covers the wound with the improvement of granulation tissues. Diabetic wounds continue to be in the inflammatory phase ensuing in the inhibition of the formation of matured granulation tissue and reduces injury tensile strength. This is triggered through vascular injury leading to ischemia. The remaining segment of the wound healing technique is the maturation segment

additionally referred to as the remodelling stage. In the maturation phase, the damage is completely closed. The fibroblasts absolutely cowl the surface of the damage ensuing in tissue remodelling and the formation of a new pores and skin epidermal layer. This technique leads to wound closure that is triggered by way of the differentiation of fibroblast cells into contractile myofibroblasts.[52]

Wound dressings

Thousands of patients suffered yearly from exceptional types of epidermal or pores and skin damage or burns by way of hot water, flames, accidents, and boiling oil. These accidents usually accompany with disabilities on treatment and excessive price treatment or even now and again death. As the World Health Organization, greater than 30,000 deaths per year occur, owing to scalds and burns types.[50] Notably, each two patients' instances of adults and overage human beings are struggling over challenges that dermis regeneration can't appear spontaneously again. Since auto-skin restore has fairly accessibility and accompanied by way of in addition scarring. This typical approach for substantial loss of dermis can't meet the requirements, and polymeric dressing substances grew to become inevitable for pores and skin tissue restore or healing with time.

Until the mid-1962, the researches of wound dressing and healing have been particularly neglected. It used to be supposed in the past that the wound heal is quicker and greater efficient, if it is saved dried and maintained uncovered. This hypothesis used to be assumed earlier than establishing the perfect necessities for wound healing materials. The pioneering work of wintry weather [55] designed the first era of wound film or "dressings", the place he revealed that the epithelial restore of wounded pig pores and skin used to be at least twice in contrast to the air-exposed wounds. Since this date, the research and researches of wound dressing improvement have been in addition heightened; suggesting perfect wound dressings need to keep a wetted surroundings with excessive biocompatibility and prohibit the bacterial infection for accelerating the tissue regeneration. In eighties, the wound dressings have been categorized in accordance to their wettability degree into dried and wet dressings.

Table 1. Commercial hydrogel-based dressing available on the market.

Commercial wound dressings	**Composition**	**Aplication**
GranuGel^{R}	Hydrogel-based skin dressing that ensures a moist environment in necrotic wounds	It is used in dry, sloughy and necrotic wounds such as leg ulcers and pressure sores
ActivHeal^{V}	Amorphous hydrogel that keeps moisture in the injured site	Use on dry and sloughy wounds as pressure ulcers, cavity wounds, leg ulcers, diabetic ulcers, etc.
NU-GEL^{TM}	Hydroactive hydrogel with calcium alginate. Keeps the injured area moist, helping to remove biological fluids	Recommended for application to chronic wounds, such as pressure ulcers
DermaSyn	Amorphous hydrogel dressing with vitamin E. Maintains moisture at the wound site, preventing tissue dryness.	Indicated for the treatment of light burns, abrasion, superficial cuts, etc
CutimedV^{R} Gel	Amorphus hydrogel formed by Carbomer 940, purified water, glycerol, sodium hydroxide and EDTA sodium	It is used in treatment of chronic wounds.
Purilon	PurilonVR gel is made up of purified water, sodium carboxymethylcellulose and calcium alginate.	Can be used to treat dry and crusted necrotic wounds, pressure ulcers, uninfected diabetic foot ulcers, and on 1st and 2nd degree burns.
INTRASITE^{R} Gel	A transparent hydrogel	It is indicated for the treatment of shallow and deep wounds such as pressure ulcers, leg

	composed of carboxy-methylcellulose (CMC), propylene glycol and water hydrates necrotic and flaky tissue and absorbs exudate.	ulcers, diabetic foot ulcers, wounds malignant, burn, etc.

Hydrogels

Hydrogels are 3-dimensional hydrophilic polymeric networks, of synthetic or natural origin, with a excessive capability to keep water (> 90%).[58] According to Gyles et al., this material's swelling ability is due to hydrophilic molecules (-OH, -CONH, -CONH2, and -SO3H) in the polymeric aspects of the gels. However, this property reduces their mechanical resistance, and crosslinking strategies are essential to enhance their performance. Usually, hydrogels' stabilization takes place via chemical or bodily interactions alongside the polymeric chain. Chemically crosslinked networks have everlasting junctions; bodily networks have transient bonds that occur from tangles of polymer chains or bodily interactions, such as ionic interactions, hydrogen bonds, or hydrophobic interactions. Larraneta et al. verified the effectiveness of the crosslinking technique for hydrogels' manufacturing primarily based on hyaluronic acid to enhance each dressings and devices for transporting medicines.[60–65]

Applications of Hydrogels for Wound Healing

Hydrogels characterize a type of substances that are extensively used in gentle tissue engineering of skin, blood vessel, muscle, and fats.[66] Hydrogels are 3-dimensional (3D) networks consisting of bodily or chemically crosslinked bonds of hydrophilic polymers. The insoluble hydrophilic structures show a outstanding potential to take in wound exudates and permits oxygen diffusion to accelerate healing.[67,68] Importantly, hydrogels possess a especially hydrated 3D polymeric community and can bind several-fold greater water as in contrast to their dry weight and can thereby keep a excessive moisture stage of the wound bed. Due to these special physical properties, hydrogel networks can be casted into a number of sizes and shapes. Therefore, hydrogel-based substances are the most appropriate dressings to cover pores and skin wounds. Furthermore, hydrogels provide a platform to load cells, antibacterial agents, growth factors, as properly as distinct supplementary and biomacromolecules. With regard to ECM similarity, hydrogels used for wound healing applications provide a cell-friendly 3D surroundings to promote tissue regeneration, with or except the presence of cells embedded in the scaffold. Importantly, all hydrogels need to satisfy the fundamental requirements of biocompatibility in scientific use as properly as possess unique physical and mechanical properties perfect for pores and skin wound functions. Moreover, they also need to provide the excellent microenvironment for vessel ingrowth and cellular proliferation.[69,70]

Many research projects are now focusing on the improvement of new devices for wound management. There are some essential components that ought to be current in the perfect wound care system. It is very essential to keep most beneficial humidity at the wound site due to the fact if the surface becomes dry, it will be greater difficult for the nutrients to reach the region and additionally the immune defences of the wound surface would come to be impaired, as it will take greater time to reach the wound surface. The product need to be non-toxic and non-allergenic so that it would now not motive any immune response at the wound site. It is additionally essential now not to purpose any damage at the wound site following the removal; it ought to be resistant to bacteria, ought to permit gaseous and water vapour exchange and it need to be low cost at a massive scale. Thus, one of the most used functions is the use of hydrogels for wound treatment.[70]

Hydrogels containing antibiotics are now used in quite a few wound conditions, due to the fact of the potential of the hydrogel to be non-toxic, to have excessive water content, excessive oxygen permeability, extended biocompatibility, ease of loading and releasing drugs, structural variety and to now not reason any immune response at the wound site. Hydrogels can be used for the delivery of stem cells to the wound site. They are an appealing alternative as conveyance vehicles, as they increment the time span that stem cells stay at a wound site. This property emerges from the potential of sure hydrogels to bring up cell bonds and to have interaction stem cells activity with the aid of supporting the preservation of their regular aggregate. These highlights are fortified by means of in vitro preculture of stem cells internal hydrogels, as exhibited by way of the presence of relocated cells in the wound site for intervals longer than eleven days post-transplantation. another application of hydrogels is the delivery of bioactive agents like heparin, hyaluronic acid or ibuprofen. The properties needed by way of a exact hydrogel are safety, antimicrobial resistance, drug loading ability and easy drug release. It have to have the potential to keep its properties for a long time, as some wounds would require treatment for a lengthy period.[69]

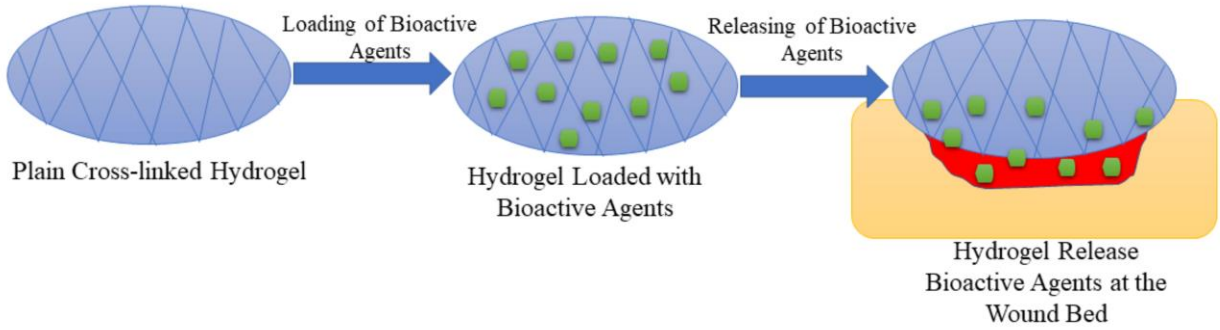


Figure 4: Cross-linked hydrogel loaded with bioactive agents

Chitosan:

Chitosan is a biodegradable polymer received from the deacetylation of chitin and can be cross-linked physically or chemically. Their amino and hydroxyl busines permit structural changes, with getting chitosan hydrogels by using polymer solubilization in an acidic aqueous medium. Chitosan's biocompatibility, nontoxicity, homeostatic effect, and biodegradability are appropriate for pores and skin dressing applications. Furthermore, this polymer prevents feasible tissue infections, contributing to optimizing the recuperation technique, and has a direct effect all through healing ranges (homeostasis, inflammation, proliferation, and remodeling). It promotes the migration and infiltration of macrophages and neutrophils. As a result, the damage is averted from contacting exterior agents (microorganisms), contributing to reepithelization optimization. Furthermore, chitosan favors that the scar at the lesion site minimizes, assisting the remodeling segment. Alginate/chitosan-based hydrogel, for example, was once studied by way of Bagher et al. to be used in the cure of pores and skin wounds, the use of distinctive concentrations of hesperidin. Takei et al. said in their lookup that they have been capable to strengthen chitosangluconic acid (CG) via physical crosslinking for wound treatment. This material underwent an autoclave sterilization method to verify its applicability as a wound dressing.[71–75]

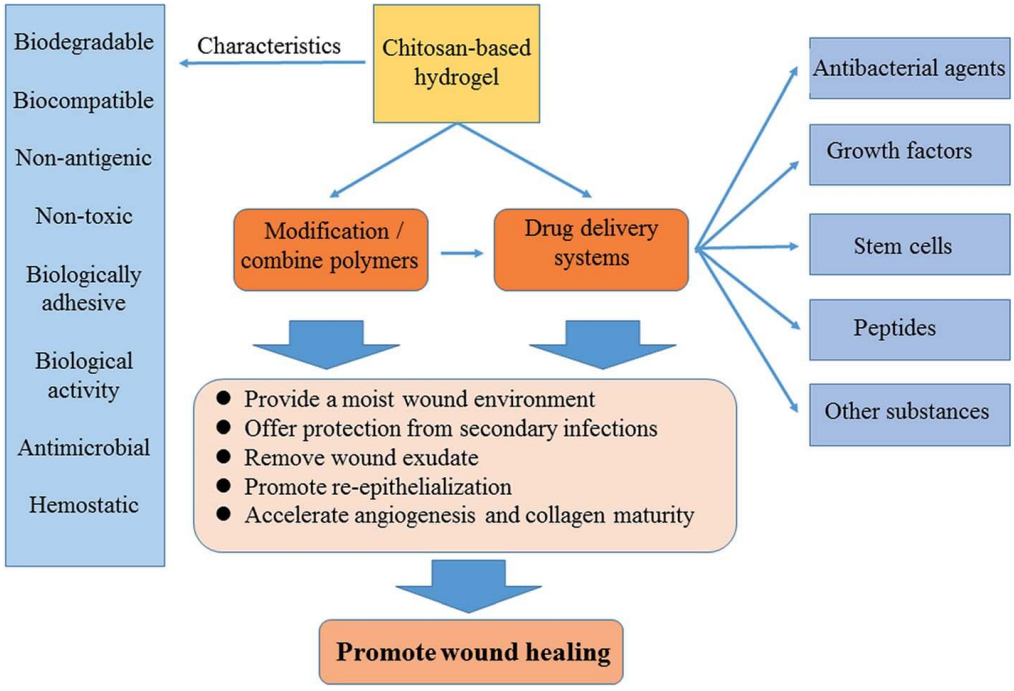


Figure 5: Application of chitosan-based hydrogel dressings

Polyethylene glycol (PEG):

Polyethylene glycol is viewed one of the great biocompatible synthetic polymers in the scientific field. It is soluble in water and a massive phase of organic solvents. Its mechanical and thermal properties can

be stabilized thru copolymerization with different polymers, such as chitosan. Moreover, PEG hydrogels are nonimmunogenic, nontoxic, and have hydrophilic properties. In the research, a dressing used to be developed via the crosslinking between PEG and chitosan, containing growth elements (GF). The maintenance of the therapeutic degrees of GF's at the damage site used to be verified. Masood et al. synthesized a chitosan-poly ethylene glycol (PEG) hydrogel, impregnated with silver nanoparticles (AgNP), to be used in persistent wounds of diabetic patients. The consequences confirmed wonderful antibacterial and antioxidant properties of AgNP loaded chitosan PEG hydrogels, which have been later applied to deal with diabetic rat wounds. In addition, the researchers found that the material absorbed a satisfactory quantity of fluid, had greater porosity, and had a greater water vapor transition rate (WVTR) for samples that contained the presence of AgN.[77–79]

Alginate:

Alginate is a biopolymer with hydrophilic, biocompatible, biodegradable, and nontoxic properties. Furthermore, it is an anionic polysaccharide from herbal origin, containing ß-D-manuronic acid and a-L-guluronic acid in its polymeric chain. It is frequently determined in the cell wall of brown algae and can also be synthesized by means of microbial fermentation (bacteria Pseudomonas aeruginosa, for example). Due to its hydrophilic capacity and desirable elasticity, it is viewed an extremely good material for application as a pores and skin dressing. It can take in a considerable quantity of biological fluids from the injured site. Alginate dressings can be synthesized, both by means of ionic crosslinking or through solutions with magnesium, zinc, and calcium, however it is additionally interesting to observe that alginate has its physicochemical properties optimized when it is crosslinked with different polymers. The consequences confirmed that CaCl2 optimized the mechanical characteristics, however on the different hand, it impaired the fluid absorption properties. Furthermore, curcumin-b-cyclodextrin introduced to the material used to be superb in opposition to Gram-negative (Escherichia coli) and Gram-positive micro-organism (Staphylococcus aureus). The in vitro assay verified the nontoxicity of the material.[79–85]

Gelatin

Gelatin is a biopolymer obtained by means of collagen hydrolysis. It is broadly used as a wound dressing due to its property of cell adhesion and proliferation, biocompatibility, and nontoxicity. In addition, it is considered the most considerable protein in the animal kingdom and can be categorized as bovine, porcine, or fish gelatin. As a dressing, gelatin favors a appropriate surroundings for tissue growth and indicates similarities with the extracellular matrix. However, this fabric has fragile mechanical properties, which can be increased by way of copolymerization with different polymers. Research through Liu et al. confirmed a new kind of hydrogel primarily based on poly(aglutamic acid) (c-PGA)/gelatin cross-linked with oligomeric proanthocyanidins (OPCs). The material evaluation confirmed appropriate fluid swelling capacity; in addition, it used to be possible to observe the growth of fibroblasts and anti-oxidation, confirming crosslinking with OPCs. Moreover, tests carried out on rats confirmed an acceleration in wound healing, indicating that this hydrogel can be utilized as a pores and skin dressing. In some other study, Mao et al. synthesized an oxidized starch/gelatin-based shape memory hydrogel with self-contraction to facilitate the treatment of pores and skin wounds. The structure memory used to be developed with the aid of introducing Schiff-based constructions (-N ¼ C) into the polymer structure. This hydrogel confirmed some excellent results.[86–91]

Poly(vinyl alcohol) (PVA)

Poly(vinyl alcohol) is one of the essential polymers used for wound treatment. It is a transparent biocompatible material with hydrophilic properties and can hold the injured surroundings moist. However, due to its low elasticity and mechanical properties, many researchers crosslink PVA with different polymers, enhancing its characteristics. The used crosslinking techniques with PVA hydrogels are physical and chemical. Strong hydrogen bonds are formed in the polymer chain except poisonous chemical residues in physical crosslink. Covalent bonds are created with the hydroxyl group (-OH) existing in the PVA chain to chemical crosslink. Nonetheless, this approach can go away traces of toxic residues, which ought to negatively interfere with materials for scientific application.[92–97]

Cellulose

Cellulose is characterized as the most plentiful polysaccharide current in the ecosystem. It has interesting characteristics to treat wounds (biodegradability, appropriate mechanical properties, and biocompatibility).[76] Both plant life and microorganisms can produce it, keeping the identical chemical structure (b-1,4-D(þ)-glucopyranose linked to 1,4-glycosidic, forming a lengthy chain). Shefa et al.[98] synthesize a multifunctional hydrogel primarily based on PVA/TEMPO-oxidized cellulose nanofiber intercalated with curcumin (TOCN-PVA-Cur). The results showed that the extend in material viscosity used to be immediately linked with PVA concentration in the

sample. Furthermore, in biological assays, it was once viable to examine wound closure in rats within two weeks.

Carboxymethyl cellulose (CMC)

Carboxymethylcellulose is a cellulose derivative in its chemical structure, the partial modification of the hydroxyl group with the aid of carboxymethyl. In addition, CMC has interesting properties for application in the manufacture of dressings, as it is a biodegradable, biocompatible, nontoxic, and hydrophilic material. In the work of Capanema et al. , new types of hydrogel membranes have been synthesized for application as a skin dressing. First, the material used to be developed the use of exclusive degrees of carboxymethyl, and then it was once combined with polyethylene glycol (PEG). The analysis indicated that the material was once capable to soak up a considerable quantity of fluid ranging from a hundred percent to 5000% and confirmed proper cell viability. Furthermore, the structural results bought via the FTIR established that the hydrogel contained a hybrid structure (amorphous shape of CMC and semi-crystalline structure of PEG), confirming the crosslinking process. [76]

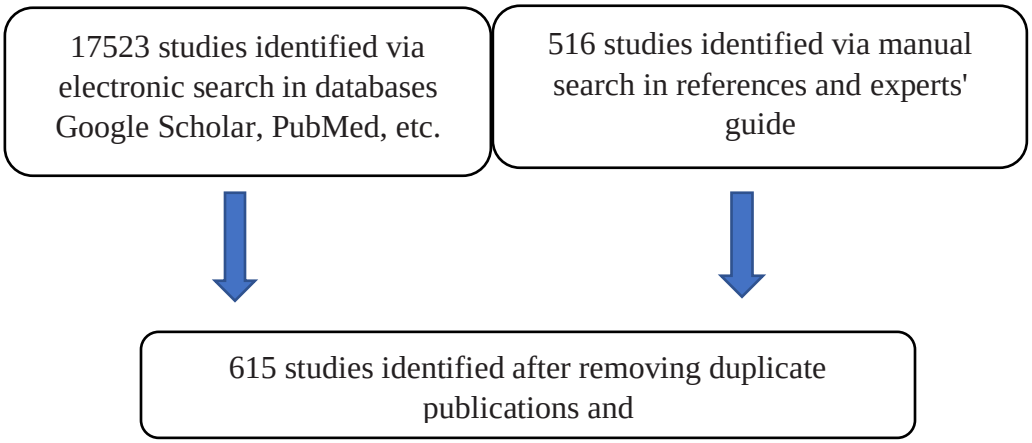
Table 2: Characteristics, effects and applications of hydrogels

Types of hydrogels/ applications	**Basic material**	**Hydrogel fabrication pathways**	**Hydrogel effect/property**	**References**
Hydrogels containing antibiotics	Polyethylene glycol (PEG)	Conjugated DNA oligonucleotides to polyethylene glycol using free radical polymerization and tetracycline	Tetracycline could inhibit bacterial growth within 48 h and induce the formation of zones of inhibition on the agar plate.	99
	Keratin hydrogels	Lyophilized oxidized keratin was weighed and hydrated with ciprofloxacin	Burns treated with ciprofloxacin- keratin hydrogels Contained significantly less Pseudomonas aeruginosa and Staphylococcus aureus	100
	Polyvinyl alcohol-gelatin (PVA)	Gentamicin and serratiopeptidase were incorporated into PVAgelatin hydrogel	Natural debridement by hydrating necrotic tissue with loosening and absorbing slough and exudate in wounds. It also encourages autolytic debridement	101
Hydrogels used for the delivery of stem cells	Adipose Extracellular Matrix (ECM), Methylcellulose (MC)	ECM solution prepared by the dilution of lyophilized ECM in phosphate-buffered saline solution (PBS), while MC was prepared by dispersion technique	Accelerated wound closure, re-epithelialization, neovascularization	102
	Collagen- Polyethylene glycol, fibrin	Debrided skin adipose stem cells mixed with collagen and then PEG was added to the collagen, followed by the addition of fibrin	Less wound contraction Dermal matrix deposition	103
	Pullulan collagen	Pullulan-collagen were added to Adipose-derived mesenchymal	Accelerated wound closure, improve cell recruitment and functionality, neovascularization	104

		stem cells suspended in growth media using a capillary force method		
	Pluronic F127	Pluronic F127 powder was dissolved in PBS before encapsulation of allogeneic non-diabetic adipose-derived stem cells	Angiogenesis resulted from the cells in the hydrogel cell proliferation, accelerated wound closure, regeneration of granulation tissue	105
	Chitosan and gelatin	8 ml of 2% chitosan mixed with 2 ml of 2%/4% gelatin solution. Adipose-derived stem cells were encapsulated in the chitosan-gelatin hydrogel	Faster cell migration at the wound site, angiogenesis, higher capillary density	106
Smart hydrogels stimuli-responsive hydrogels	Aldehyde hyaluronic acid (A-HA) / adipic acid dihydrazide graft hyaluronic acid (HA-ADH) / sisomicin sulphate (SS) hydrogel	Evenly mixing A-HA, HA-ADH and SS	pH- and HAase-dependent degradability that enables the release of more aminoglycosides-SS for on-demand and sustained anti-infection and antioxidant activity	107
	Sodium alginate/poly (N-vinyl caprolactam)	N-vinyl caprolactam polymerized in an aqueous sodium alginate followed by chemical and ionic crosslinking. Tannic acid incorporated hydrogels were also fabricated	Temperature-pH dual responsive hydrogel with excellent free radical scavenging, anti-inflammatory, antibacterial effect	108
	Alginate/polyacrylamide hydrogel matrix	Phenol red was modified with methacrylate to allow copolymerization with the hydrogel matrix	The colour of the hydrogel changes from yellow (pH 5,6 and 7) to orange (7.4 and 8), and finally to red (pH 9). This range of colour change matches the clinically meaningful pH range of chronic or infected wounds	109
	Sodium alginate/bioglass composite hydrogel	Sodium alginate (SA) microparticles containing conditioned medium (CM) of cells (SACM). Inside the SACM microparticles, poly(lactic-co-glycolic acid) microspheres containing pirfenidone were encapsulated	The hydrogel system sequentially delivers bioactive molecules for meeting the biologic requirements and timeline of each wound healing stage	109

Hydrogels used for the delivery of bioactive agents	Mixture of polyvinyl acetate (PVA), gelatin and chitosan	3% chitosan solution prepared in a 3% acetic acid solution; PVA was dissolved in distilled water; 5% gelatin solution dissolved in distilled water. Gel mixture was prepared in a ratio of 2:1:1 of chitosan/PVA/gelatin	Accelerated wound closure, re-epithelization; faster transition from the inflammatory to the maturation phase, enhanced collagen deposition, myofibroblasts and vessel formation	107
	Polyvinylpyrrolidone/polyethylene glycol-dimethacrylate (PVP/ PEG-DMA)	Cyclodextrins (CD) attached to the PVP/PEG-DMA	β-CDs immobilized in the PVP/PEG-DMA matrix stimulated a prolonged release of ibuprofen	108
	Heparin Poloxamer	Heparin–poloxamer (HP) conjugate was prepared with Ethylene dichloride/N-hydroxysuccinimide (EDC/NHS) as coupling agents and then HP with growth factor Acid fibroblast growth factor (aFGF) hydrogels and HP-with growth factor Basic fibroblast growth factor (bFGF) hydrogels were prepared by lyophilizing HP powder and mixing it with aFGF / bFGF	Improved wound closure, re-epithelialization	109
	PEG and heparin	40% thiolated heparin and 6 kilodalton (kDa) PEG in a 1:1 ratio was dissolved in PBS	Advanced granulation tissue formation, capillary formation, and re epithelialization	109

Systematic Review



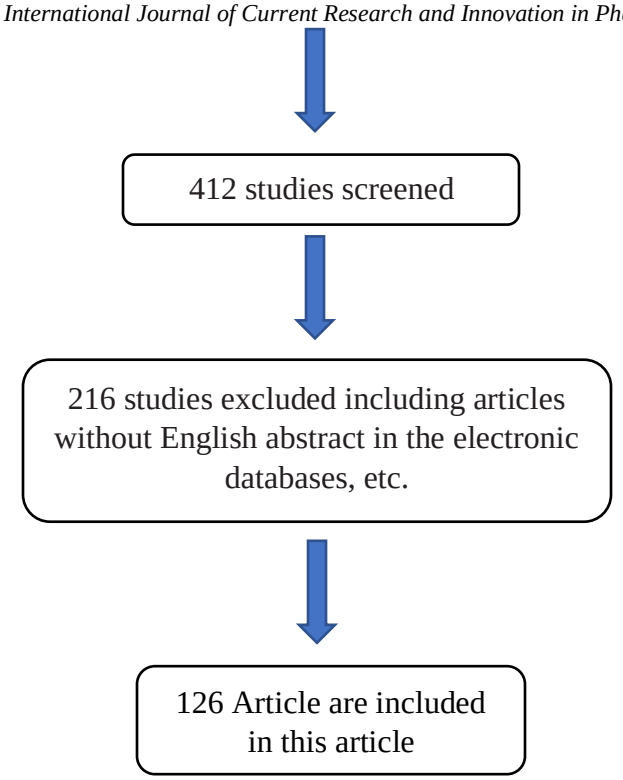


Figure 6: Flow diagram for the study review

CONCLUSIONS AND FUTURE PERSPECTIVES:

Almost all of us has confronted an open wound for the duration of his life. Most of these wounds had been treated effortlessly while different wanted clinical attention. Wound management is amongst most substantial clinical area given that infected wound can lead to serious complication. In this review, authors aimed to conclude the current information of wound management and Hydrogels primarily based wound healing. Hydrogel appear to be greater perfect for the improvement of the ideal wound dressing, due to their many beneficial properties and versatility. The development of dressings that should suit all types of wounds is still very hard to imagine, and the secret of therapeutic success of patients with wounds lies in the information of medical staff about the pathophysiology of wounds and treatment options. Development of new technologies and elevated get entry to to them in clinical exercise bring new treatment resources for patients however their successful use requires a appropriate information of therapeutic indications. Recently, hydrogel-based wound dressings have emerged as convenient scaffolds for wound care due to their versatile properties. Numerous research studies additionally indicate substantial and growing interest in the synthesis and fabrication of such hydrogels and growing new “in situ” forming “smart” nanocomposite hydrogels for a number of biomedical applications. Additionally, understanding and regulating the interactions between polymeric chains and cells will inspire future research of nanocomposite hydrogels.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests.

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REFERENCES:

1. Nussbaum SR, Carter MJ, Fife CE, et al. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. Value in Health. 2018;21(1):27-32. doi:10.1016/j.jval.2017.07.007

2. Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. Int Wound J. 2016;13(Suppl 2):5-15. doi:10.1111/iwj.12623

3. Francesko A, Petkova P, Tzanov T. Hydrogel Dressings for Advanced Wound Management. Curr Med Chem. 2019;25(41):5782-5797. doi:10.2174/0929867324666170920161246

4. Logan G. Clinical judgment and decision making in wound assessment and management: is experience enough? Br J Community Nurs. 2015;Wound Care. doi:10.12968/bjcn.2015.20.sup3.s21

5. Carlson BM, Elsevier Science (Firm). Human Embryology and Developmental Biology.

6. McGrath JA, Uitto J. Structure and Function of the Skin. :1-52. doi:10.1002/9781118441213.RTD0002

7. Drake RL, Vogl AW, Adam WMM. Gray's Antomy for Students. Published online 2020:582-612.

8. Driskell RR, Lichtenberger BM, Hoste E, et al. Distinct fibroblast lineages determine dermal architecture in skin development and repair. Nature. 2013;504(7479):277-281. doi:10.1038/nature12783

9. Rook's textbook of dermatology (Book, 2016) [WorldCat.org]. Accessed May 5, 2022. https://www.worldcat.org/title/rooks-textbook-of-dermatology/oclc/930014455?referer=di&ht=edition

10. Cumberbatch M, Dearman RJ, Griffiths CEM, Kimber I. Epidermal Langerhans cell migration and sensitisation to chemical allergens. APMIS. 2003;111(7-8):797-804. doi:10.1034/j.1600-0463.2003.11107811.x

11. Natsuga K. Epidermal barriers. Cold Spring Harb Perspect Med. 2014;4(4). doi:10.1101/cshperspect.a018218

12. Stan D, Tanase C, Avram M, et al. Wound healing applications of creams and "smart" hydrogels. Exp Dermatol. 2021;30(9):1218-1232. doi:10.1111/exd.14396

13. Stecco C, Pirri C, Fede C, et al. Dermatome and fasciatome. Clinical Anatomy. 2019;32(7):896-902. doi:10.1002/ca.23408

14. Turner CT, Hiroyasu S, Granville DJ. Granzyme B as a therapeutic target for wound healing. Expert Opin Ther Targets. 2019;23(9):745-754. doi:10.1080/14728222.2019.1661380

15. Stan D, Tanase C, Avram M, et al. Wound healing applications of creams and "smart" hydrogels. Exp Dermatol. 2021;30(9):1218-1232. doi:10.1111/exd.14396

16. Dabrowska AK, Rotaru GM, Derler S, et al. Materials used to simulate physical properties of human skin. Skin Research and Technology. 2016;22(1):3-14. doi:10.1111/srt.12235

17. Dąbrowska 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(2):165-174. doi:10.1111/srt.12424

18. Feingold KR. Lamellar bodies: The key to cutaneous barrier function. Journal of Investigative Dermatology. 2012;132(8):1951-1953. doi:10.1038/jid.2012.177

19. Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. Annu Rev Chem Biomol Eng. 2017;8:177-200. doi:10.1146/annurev-chembioeng-060816-101514

20. Yousef H, Sharma S. Anatomy, Skin (Integument), Epidermis. StatPearls Publishing; 2018. Accessed May 5, 2022. http://www.ncbi.nlm.nih.gov/pubmed/29262154

21. Kim HS, Sun X, Lee JH, Kim HW, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. Adv Drug Deliv Rev. 2019;146:209-239. doi:10.1016/j.addr.2018.12.014

22. Hilchie AL, Wuerth K, Hancock REW. Immune modulation by multifaceted cationic host defense (antimicrobial) peptides. Nat Chem Biol. 2013;9(12):761-768. doi:10.1038/nchembio.1393

23. Schmid-Wendtner MH, Korting HC. The pH of the skin surface and its impact on the barrier function. Skin Pharmacol Physiol. 2006;19(6):296-302. doi:10.1159/000094670

24. Kleesz P, Darlenski R, Fluhr JW. Full-body skin mapping for six biophysical parameters: Baseline values at 16 anatomical sites in 125 human subjects. Skin Pharmacol Physiol. 2011;25(1):25-33. doi:10.1159/000330721

25. Bäsler K, Bergmann S, Heisig M, Naegel A, Zorn-Kruppa M, Brandner JM. The role of tight junctions in skin barrier function and

dermal absorption. Journal of Controlled Release. 2016;242:105-118. doi:10.1016/j.jconrel.2016.08.007

26. Hachem JP, Roelandt T, Schürer N, et al. Acute acidification of stratum corneum membrane domains using polyhydroxyl acids improves lipid processing and inhibits degradation of corneodesmosomes. Journal of Investigative Dermatology. 2010;130(2):500-510. doi:10.1038/jid.2009.249

27. Deal HE, Brown AC, Daniele MA. Microphysiological systems for the modeling of wound healing and evaluation of pro-healing therapies. J Mater Chem B. 2020;8(32):7062-7075. doi:10.1039/d0tb00544d

28. Okur ME, Karantas ID, Şenyiğit Z, Üstündağ Okur N, Siafaka PI. Recent trends on wound management: New therapeutic choices based on polymeric carriers. Asian J Pharm Sci. 2020;15(6):661-684. doi:10.1016/j.ajps.2019.11.008

29. Coalson E, Bishop E, Liu W, et al. Stem cell therapy for chronic skin wounds in the era of personalized medicine: From bench to bedside. Genes Dis. 2019;6(4):342-358. doi:10.1016/j.gendis.2019.09.008

30. Koehler J, Brandl FP, Goepferich AM. Hydrogel wound dressings for bioactive treatment of acute and chronic wounds. Eur Polym J. 2018;100:1-11. doi:10.1016/j.eurpolymj.2017.12.046

31. Boateng J, Catanzano O. Advanced Therapeutic Dressings for Effective Wound Healing - A Review. J Pharm Sci. 2015;104(11):3653-3680. doi:10.1002/jps.24610

32. Zhang A, Liu Y, Qin D, Sun M, Wang T, Chen X. Research status of self-healing hydrogel for wound management: A review. Int J Biol Macromol. 2020;164:2108-2123. doi:10.1016/j.ijbiomac.2020.08.109

33. Gholipourmalekabadi M, Sapru S, Samadikuchaksaraei A, Reis RL, Kaplan DL, Kundu SC. Silk fibroin for skin injury repair: Where do things stand? Adv Drug Deliv Rev. 2020;153:28-53. doi:10.1016/j.addr.2019.09.003

34. Gupta A, Kowalczuk M, Heaselgrave W, Britland ST, Martin C, Radecka I. Title: Production and Application of Hydrogels in Wound Management: A Review.

35. Felgueiras HP, Amorim MTP. Functionalization of electrospun polymeric wound dressings with antimicrobial peptides. Colloids Surf B Biointerfaces. 2017;156:133-148. doi:10.1016/j.colsurfb.2017.05.001

36. Satish A, Aswathi R, Caroline Maria J, Sai Korrapati P. Triiodothyronine impregnated alginate/gelatin/polyvinyl alcohol composite scaffold designed for exudate-intensive wound therapy. Eur Polym J. 2019;110:252-264. doi:10.1016/j.eurpolymj.2018.11.032

37. Opdenakker G, van Damme J, Vranckx JJ. Immunomodulation as Rescue for Chronic Atonic Skin Wounds. Trends Immunol. 2018;39(4):341-354. doi:10.1016/j.it.2018.01.010

38. Tyavambiza C, Dube P, Goboza M, Meyer S, Madiehe AM, Meyer M. Wound healing activities and potential of selected african medicinal plants and their synthesized biogenic nanoparticles. Plants. 2021;10(12). doi:10.3390/plants10122635

39. 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

40. Dattani R, Farouk R. Wound Classification. In: Principles of Surgery Vivas for the MRCS. Cambridge University Press; 2010:323-328. doi:10.1017/cbo9780511663482.020

41. Yu R, Zhang H, Guo B. Conductive Biomaterials as Bioactive Wound Dressing for Wound Healing and Skin Tissue Engineering. Nanomicro Lett. 2022;14(1). doi:10.1007/s40820-021-00751-y

42. Wallace HA, Zito PM. Wound Healing Phases. StatPearls Publishing; 2019. Accessed May 6, 2022. http://www.ncbi.nlm.nih.gov/pubmed/29262065

43. Gonzalez ACDO, Andrade ZDA, Costa TF, Medrado ARAP. Wound healing - A literature review. An Bras Dermatol. 2016;91(5):614-620. doi:10.1590/abd1806-4841.20164741

44. Ye X, Wang Z, Zhang X, Zhou M, Cai L. Hemocompatibility research on the micro-structure surface of a bionic heart valve. In: Bio-Medical Materials and Engineering. Vol 24. IOS Press; 2014:2361-2369. doi:10.3233/BME-141049

45. Bonar RA, Lippi G, Favaloro EJ. Overview of hemostasis and thrombosis and contribution of laboratory testing to diagnosis and management of hemostasis and thrombosis disorders. In: Methods in Molecular Biology. Vol 1646. Humana Press Inc.; 2017:3-27. doi:10.1007/978-1-4939-7196-1_1

46. Versteeg HH, Heemskerk JWM, Levi M, Reitsma PH. New Fundamentals in hemostasis. Physiol Rev. 2013;93(1):327-358. doi:10.1152/physrev.00016.2011

47. Rossaint J, Margraf A, Zarbock A. Role of platelets in leukocyte recruitment and resolution of inflammation. Front Immunol. 2018;9(NOV):2712. doi:10.3389/fimmu.2018.02712

48. Puhaindran ME. Principles of wound healing. In: Diabetic Foot Problems. World Scientific Publishing Co.; 2008:395-402. doi:10.1142/9789812791535_0028

49. Bowden LG, Byrne HM, Maini PK, Moulton DE. A morphoelastic model for dermal wound closure. Biomech Model Mechanobiol. 2016;15(3):663-681. doi:10.1007/s10237-015-0716-7

50. desJardins-Park HE, Foster DS, Longaker MT. Fibroblasts and wound healing: an update. Regenerative Med. 2018;13(5):491-495. doi:10.2217/rme-2018-0073

51. Midwood KS, Williams LV, Schwarzbauer JE. Tissue repair and the dynamics of the extracellular matrix. International Journal of Biochemistry and Cell Biology. 2004;36(6):1031-1037. doi:10.1016/j.biocel.2003.12.003

52. Alven S, Peter S, Mbese Z, Aderibigbe BA. Polymer-Based Wound Dressing Materials Loaded with Bioactive Agents: Potential Materials for the Treatment of Diabetic Wounds. Polymers (Basel). 2022;14(4):724. doi:10.3390/polym14040724

53. Jones A, Vaughan D. Hydrogel dressings in the management of a variety of wound types: A review. Journal of Orthopaedic Nursing. 2005;9(SUPPL. 1):S1-S11. doi:10.1016/S1361-3111(05)80001-9

54. Powers JG, Higham C, Broussard K, Phillips TJ. Wound healing and treating wounds. J Am Acad Dermatol. 2016;74(4):607-625. doi:10.1016/j.jaad.2015.08.070

55. Aswathy SH, Narendrakumar U, Manjubala I. Commercial hydrogels for biomedical applications. Heliyon. 2020;6(4):e03719. doi:10.1016/j.heliyon.2020.e03719

56. Jaffe L, Wu SC. Dressings, Topical Therapy, and Negative Pressure Wound Therapy. Clin Podiatr Med Surg. 2019;36(3):397-411. doi:10.1016/j.cpm.2019.02.005

57. Cascone S, Lamberti G. Hydrogel-based commercial products for biomedical applications: A review. Int J Pharm. 2020;573. doi:10.1016/j.ijpharm.2019.118803

58. Finnegan S, Percival SL. Clinical and Antibiofilm Efficacy of Antimicrobial Hydrogels. Adv Wound Care (New Rochelle). 2015;4(7):398-406. doi:10.1089/wound.2014.0556

59. The properties of hydrogel dressings and their impact on wound healing | Nursing Times. Accessed May 6, 2022. https://www.nursingtimes.net/archive/the-properties-of-hydrogel-dressings-and-their-impact-on-wound-healing-01-01-2004/

60. Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. J Adv Res. 2015;6(2):105-121. doi:10.1016/j.jare.2013.07.006

61. Parhi R. Cross-linked hydrogel for pharmaceutical applications: A review. Adv Pharm Bull. 2017;7(4):515-530. doi:10.15171/apb.2017.064

62. Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science (1979). 2017;356(6337). doi:10.1126/science.aaf3627

63. Rizwan M, Yahya R, Hassan A, et al. pH sensitive hydrogels in drug delivery: Brief history, properties, swelling, and release mechanism, material selection and applications. Polymers (Basel). 2017;9(4). doi:10.3390/polym9040137

64. Gyles DA, Castro LD, Silva JOC, Ribeiro-Costa RM. A review of the designs and prominent biomedical advances of natural and synthetic hydrogel formulations. Eur Polym J. 2017;88:373-392. doi:10.1016/j.eurpolymj.2017.01.027

65. Nikolova MP, Chavali MS. Recent advances in biomaterials for 3D scaffolds: A review. Bioact Mater. 2019;4:271-292. doi:10.1016/j.bioactmat.2019.10.005

66. Nicodemus GD, Bryant SJ. Cell encapsulation in biodegradable hydrogels for tissue engineering applications. Tissue Eng Part B Rev. 2008;14(2):149-165. doi:10.1089/ten.teb.2007.0332

67. Kumar A, Jaiswal M. Design and in vitro investigation of nanocomposite hydrogel based in situ spray dressing for chronic wounds and synthesis of silver nanoparticles using green chemistry. J Appl Polym Sci. 2016;133(14):n/a-n/a. doi:10.1002/app.43260

68. Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. Wound healing dressings and drug delivery systems: A review. J Pharm Sci. 2008;97(8):2892-2923. doi:10.1002/jps.21210

69. Jones A, Vaughan D. Hydrogel dressings in the management of a variety of wound types: A review. Journal of Orthopaedic Nursing. 2005;9(SUPPL. 1):S1-S11. doi:10.1016/S1361-3111(05)80001-9

70. Tavakoli S, Mokhtari H, Kharaziha M, Kermanpur A, Talebi A, Moshtaghian J. A multifunctional nanocomposite spray dressing of Kappa-carrageenan-polydopamine modified ZnO/L-glutamic acid for diabetic wounds. Materials Science and Engineering C. 2020;111. doi:10.1016/j.msec.2020.110837

71. Matica MA, Aachmann FL, Tøndervik A, Sletta H, Ostafe V. Chitosan as a wound dressing starting material: Antimicrobial properties and mode of action. Int J Mol Sci. 2019;20(23). doi:10.3390/ijms20235889

72. Frank LA, Onzi GR, Morawski AS, Pohlmann AR, Guterres SS, Contri R v. Chitosan as a coating material for nanoparticles intended for biomedical applications. React Funct Polym. 2020;147. doi:10.1016/j.reactfunctpolym.2019.104459

73. Miguel SP, Moreira AF, Correia IJ. Chitosan based-asymmetric membranes for wound healing: A review. Int J Biol Macromol. 2019;127:460-475. doi:10.1016/j.ijbiomac.2019.01.072

74. Ranjith R, Balraj S, Ganesh J, John Milton MC. Therapeutic agents loaded chitosan-based nanofibrous mats as potential wound dressings: A review. Mater Today Chem. 2019;12:386-395. doi:10.1016/j.mtchem.2019.03.008

75. Kalantari K, Afifi AM, Jahangirian H, Webster TJ. Biomedical applications of chitosan electrospun nanofibers as a green polymer – Review. Carbohydr Polym. 2019;207:588-600. doi:10.1016/j.carbpol.2018.12.011

76. Lima T de P de L, Passos MF. Skin wounds, the healing process, and hydrogel-based wound dressings: a short review. J Biomater Sci Polym Ed. 2021;32(14):1910-1925. doi:10.1080/09205063.2021.1946461

77. Peng Z, Ji C, Zhou Y, Zhao T, Leblanc RM. Polyethylene glycol (PEG) derived carbon dots: Preparation and applications. Appl Mater Today. 2020;20:100677. doi:10.1016/j.apmt.2020.100677

78. Vijayan A, Sabareeswaran A, Kumar GSV. PEG grafted chitosan scaffold for dual growth factor delivery for enhanced wound healing. Sci Rep. 2019;9(1). doi:10.1038/s41598-019-55214-7

79. Masood N, Ahmed R, Tariq M, et al. Silver nanoparticle impregnated chitosan-PEG hydrogel enhances wound healing in diabetes induced rabbits. Int J Pharm. 2019;559:23-36. doi:10.1016/j.ijpharm.2019.01.019

80. Ullah S, Chen X. Fabrication, applications and challenges of natural biomaterials in tissue engineering. Appl Mater Today. 2020;20. doi:10.1016/j.apmt.2020.100656

81. Cao L, Lu W, Mata A, Nishinari K, Fang Y. Egg-box model-based gelation of alginate and pectin: A review. Carbohydr Polym. 2020;242. doi:10.1016/j.carbpol.2020.116389

82. Taemeh MA, Shiravandi A, Korayem MA, Daemi H. Fabrication challenges and trends in biomedical applications of alginate electrospun nanofibers. Carbohydr Polym. 2020;228. doi:10.1016/j.carbpol.2019.115419

83. Salehi M, Ehterami A, Farzamfar S, Vaez A, Ebrahimi-Barough S. Accelerating healing of excisional wound with alginate hydrogel containing naringenin in rat model. Drug Deliv Transl Res. 2021;11(1):142-153. doi:10.1007/s13346-020-00731-6

84. Aderibigbe B, Buyana B. Alginate in Wound Dressings. Pharmaceutics. 2018;10(2):42. doi:10.3390/pharmaceutics10020042

85. Zhang M, Zhao X. Alginate hydrogel dressings for advanced wound management. Int J Biol Macromol. 2020;162:1414-1428. doi:10.1016/j.ijbiomac.2020.07.311

86. Ye S, Jiang L, Su C, Zhu Z, Wen Y, Shao W. Development of gelatin/bacterial cellulose composite sponges as potential natural wound dressings. Int J Biol Macromol. 2019;133:148-155. doi:10.1016/j.ijbiomac.2019.04.095

87. Juncos Bombin AD, Dunne NJ, McCarthy HO. Electrospinning of natural polymers for the production of nanofibres for wound healing applications. Materials Science and Engineering C. 2020;114. doi:10.1016/j.msec.2020.110994

88. Lv LC, Huang QY, Ding W, Xiao XH, Zhang HY, Xiong LX. Fish gelatin: The novel potential applications. J Funct Foods. 2019;63:103581. doi:10.1016/j.jff.2019.103581

89. Mao Q, Hoffmann O, Yu K, et al. Self-contracting oxidized starch/gelatin hydrogel for noninvasive wound closure and wound healing. Mater Des. 2020;194:108916. doi:10.1016/j.matdes.2020.108916

90. Liu WC, Wang HY, Lee TH, Chung RJ. Gamma-poly glutamate/gelatin composite hydrogels crosslinked by proanthocyanidins for wound healing. Materials Science and Engineering C. 2019;101:630-639. doi:10.1016/j.msec.2019.04.018

91. Sakthiguru N, Sithique MA. Fabrication of bioinspired chitosan/gelatin/allantoin biocomposite film for wound dressing application. Int J Biol Macromol. 2020;152:873-883. doi:10.1016/j.ijbiomac.2020.02.289

92. Oliveira RN, McGuinness GB, Ramos MET, Kajiyama CE, Thiré RMSM. Properties of PVA Hydrogel Wound-Care Dressings Containing UK Propolis. Macromol Symp. 2016;368(1):122-127. doi:10.1002/masy.201500149

93. Bialik-Wąs K, Pluta K, Malina D, Barczewski M, Malarz K, Mrozek-Wilczkiewicz A. Advanced SA/PVA-based hydrogel matrices with prolonged release of Aloe vera as promising wound dressings. Materials Science and Engineering C. 2021;120. doi:10.1016/j.msec.2020.111667

94. Sukhlaaied W, Riyajan SA. Green robust pH–temperature-sensitive maleated poly(vinyl alcohol)-g-gelatin for encapsulated capsaicin. Polymer Bulletin. 2016;73(8):2303-2320. doi:10.1007/s00289-016-1609-3

95. Teodorescu M, Bercea M, Morariu S. Biomaterials of PVA and PVP in medical and pharmaceutical applications: Perspectives and challenges. Biotechnol Adv. 2019;37(1):109-131. doi:10.1016/j.biotechadv.2018.11.008

96. Kumar A, Han SS. PVA-based hydrogels for tissue engineering: A review. International Journal of Polymeric Materials and Polymeric Biomaterials. 2017;66(4):159-182. doi:10.1080/00914037.2016.1190930

97. 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

98. Shefa AA, Sultana T, Park MK, Lee SY, Gwon JG, Lee BT. Curcumin incorporation into an oxidized cellulose nanofiber-polyvinyl alcohol hydrogel system promotes wound healing. Mater Des. 2020;186:108313. doi:10.1016/j.matdes.2019.108313

99. Zhang X, Soontornworajit B, Zhang Z, Chen N, Wang Y. Enhanced loading and controlled release of antibiotics using nucleic acids as an antibiotic-binding effector in hydrogels. Biomacromolecules. 2012;13(7):2202-2210. doi:10.1021/bm3006227

100. Roy DC, Tomblyn S, Isaac KM, et al. Ciprofloxacin-loaded keratin hydrogels reduce infection and support healing in a porcine partial-thickness thermal burn. Wound Repair and Regeneration. 2016;24(4):657-668. doi:10.1111/wrr.12449

101. Singh D, Singh MR. Development of antibiotic and debriding enzyme-loaded PLGA microspheres entrapped in PVA-gelatin hydrogel for complete wound management. Artificial Cells, Blood Substitutes, and Biotechnology. 2012;40(5):345-353. doi:10.3109/10731199.2012.675337

102. Kim YH, Tabata Y. Recruitment of mesenchymal stem cells and macrophages by dual release of stromal cell-derived factor-1 and a macrophage recruitment agent enhances wound closure. J Biomed Mater Res A. 2016;104(4):942-956. doi:10.1002/jbm.a.35635

103. Natesan S, Zamora DO, Wrice NL, Baer DG, Christy RJ. Bilayer hydrogel with autologous stem cells derived from debrided human burn skin for improved skin regeneration. Journal of Burn Care and Research. 2013;34(1):18-30. doi:10.1097/BCR.0b013e3182642c0e

104. Kosaraju R, Rennert RC, Maan ZN, et al. Adipose-Derived Stem Cell-Seeded Hydrogels Increase Endogenous Progenitor Cell Recruitment and Neovascularization in Wounds. Tissue Eng Part A. 2016;22(3-4):295-305. doi:10.1089/ten.tea.2015.0277

105. Kaisang L, Siyu W, Lijun F, Daoyan P, Xian CJ, Jie S. Adipose-derived stem cells seeded in Pluronic F-127 hydrogel promotes diabetic wound healing. Journal of Surgical Research. 2017;217:63-74. doi:10.1016/j.jss.2017.04.032

106. Cheng NC, Lin WJ, Ling TY, Young TH. Sustained release of adipose-derived stem cells by thermosensitive chitosan/gelatin hydrogel for therapeutic angiogenesis. Acta Biomater. 2017;51:258-267. doi:10.1016/j.actbio.2017.01.060

107. Shamloo A, Sarmadi M, Aghababaie Z, Vossoughi M. Accelerated full-thickness wound healing via sustained bFGF delivery based on a PVA/chitosan/gelatin hydrogel incorporating PCL microspheres. Int J Pharm. 2018;537(1-2):278-289. doi:10.1016/j.ijpharm.2017.12.045

108. Wu J, Zhu J, He C, et al. Comparative Study of Heparin-Poloxamer Hydrogel Modified bFGF and aFGF for in Vivo Wound Healing Efficiency. ACS Appl Mater Interfaces. 2016;8(29):18710-18721. doi:10.1021/acsami.6b06047

109. Goh MC, Hwang Y, Tae G. Epidermal growth factor loaded heparin-based hydrogel sheet for skin wound healing. Carbohydr Polym. 2016;147:251-260. doi:10.1016/j.carbpol.2016.03.072