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A BRIEF OVERVIEW OF HYDROGELS FOR THE TREATMENT OF THE CHRONIC WOUNDS

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Abstract:

The skin is the largest organ in the human body, protecting it from the effects of the external environment. Although highly self-healing, severe skin defects do not heal on their own and must be covered with skin substitutes. Significant advances have been made in the field of skin tissue engineering in recent years for the development of new skin substitutes. This review mainly focuses on achieving the specifications of an ideal garment. This chapter discusses the use of hydrogels, both natural and synthetic, that can be used for wound healing applications. Due to its high porosity, good biocompatibility, tunable Physico-chemical properties, and benefits for wound healing, hydrogels with excellent performance have attracted extensive attention and a wide range of applications. New effective hydrogel bandages have been widely developed. In this review, after presenting several commonly used strategies for hydrogel synthesis, the most recent advances in polymer-based wound dressings are discussed. Finally, the challenges and future prospects for the development of hydrogels for wound dressings were exposed.

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

INTRODUCTION

In Europe, ~2 million humans go through chronic wounds, whilst in the United States, ~2% of the total population are estimated to be affected via chronic wounds. Doctors and nurses caring for sufferers with wounds can have a massive effect at a couple of levels, social, financial, and personal, so they must 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 [1].

This primary information will permit the patient to be correctly and efficiently evaluated so that an excellent cure plan can be chosen for him. The final aim is to have high-quality tools for wound management that will enable a clinical team of workers to diagnose, make a prognosis, is and a personalized therapy plan.

Wound recovery is a dynamic process, and the ability of the treatment plan to adapt to changes in the wound site or the patient's environment will have an important effect on recovery and quality of life. of the patient. For this reason, significant studies have been conducted on the topic of wound healing methods and wound management devices. Hydrogel dressings and creams can improve the healing process and have a beneficial effect on the result. Smart hydrogels enable real-time wound monitoring and can be used as a vehicle for the delivery of bioactive compounds [2,3].

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. 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 [4].

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 [5].

The dermis and the hypodermis are derived from the mesoderm. It consists of fibroblasts, collagen and elastic fibers, 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) [6].

At the stage of the dermis, which is a dense irregular connective tissue, there is a plentiful extracellular matrix, consisting of specialized 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 fibers. 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 [7].

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 pores and skin wound, the hypodermis does now not regenerate, being changed by way of scar tissue rich in collagen [8,9].

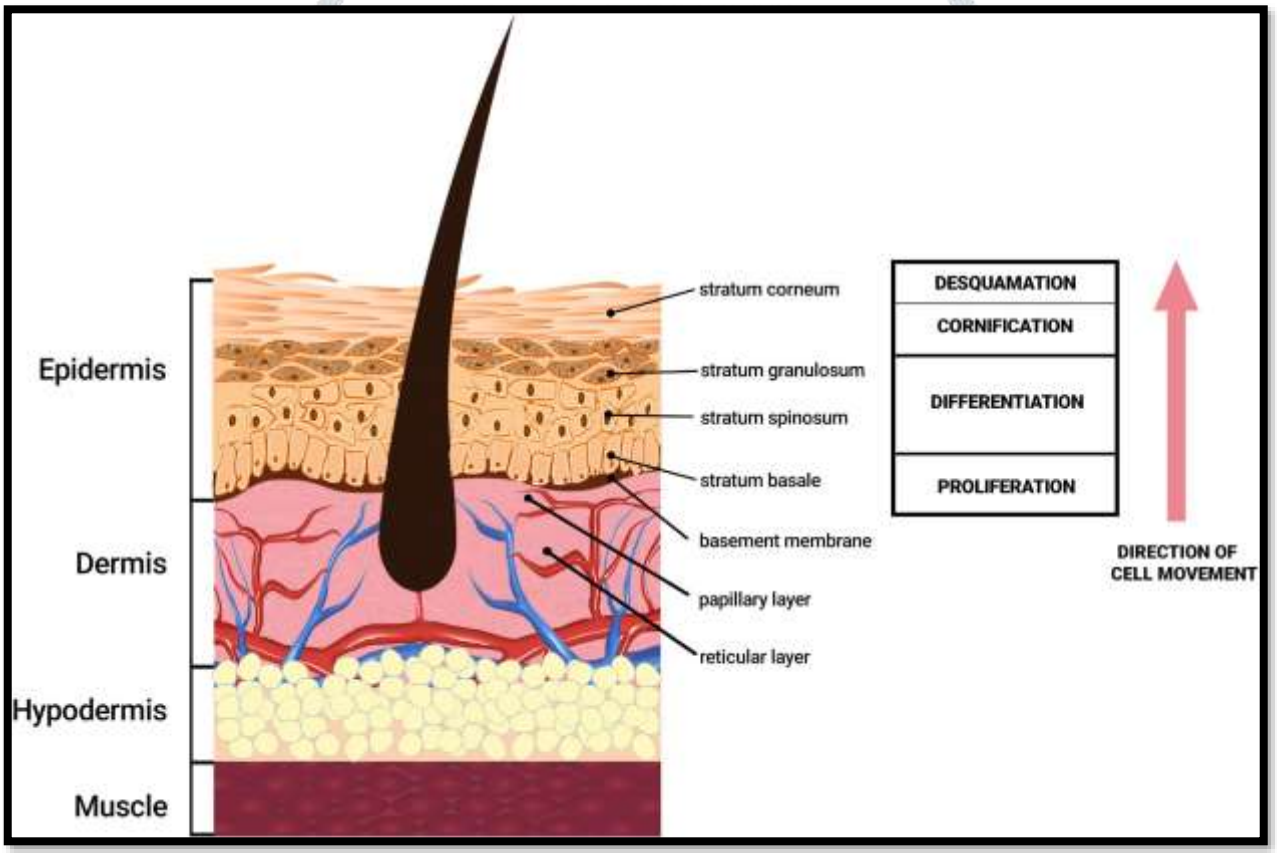

Figure 1: Basic anatomy of skin [10].

SKIN FUNCTIONS

Skin features 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 [11].

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. 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 [12].

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. 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 [13].

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 [14, 15].

Skin wounds:

The wounds manifest due to disruption of the epithelial layer and the integrity of living tissue. 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. 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. 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 [16].

However, the healing technique typically takes place, respecting the limits of the size of the wounds and the affected layers. On the other hand, continual accidents can manifest due to diabetes, stress ulcers, or perforation in arteries. One of these wounds' most important characteristics is the persistence of dead tissue in the injured region [17, 18].

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. 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 [19].

1. **Class 1:** Clean wounds are those that have not been infected. They're not infectious, don't have any inflammation, and are mostly closed. If these wounds need to be drained, a closed draining procedure is required. Furthermore, these wounds do not penetrate the pulmonary, gastrointestinal, vaginal, or urinary systems. [20].
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 [21].
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 [22].
4. **Class 4:** Wounds are seen as filthy-infected. These wounds are usually the consequence of traumatic wounds that were not appropriately cared for. Microorganisms present in perforated viscera or the operation field are the most prevalent cause of Class 4 wounds, which show devitalized tissue. [23].

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). 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 [24].

This, in turn, consequences in the activation of fibrin, which types a mesh stopping in addition bleeding. Moreover, platelets have a fundamental function in leukocyte recruitment and the initiation and growth of inflammation. 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 peptide increase factors, promoting the migration of fibroblasts into the wound site and activating angiogenesis [25].

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'.

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 [26].

Wound dressings [27]

Thousands of sufferers suffered every year from amazing kinds of epidermal or pores and pores and skin harm or burns via way of means of manner of warm water, flames, injuries, and boiling oil. These injuries commonly accompany disabilities on remedy and immoderate fee remedy or maybe on occasion death.

As the World Health Organization, extra than 30,000 deaths according to 12 months occur, thanks to scalds and burns types. Notably, every sufferer of adults and overage people is suffering from demanding situations that epidermis regeneration can`t seem spontaneously again. Since auto-pores and skin repair have pretty accessibility and are followed via way of means of manner of further scarring. This standard method for big lack of epidermis cannot meet the requirements, and polymeric dressing materials grew to come to be inevitable for pores and pores and skin tissue repair or recovery with time. Until the mid-1962, the research of wound dressing and recovery had been in particular neglected.

It was once intended withinside the beyond that the wound heal is faster and extra efficient if its miles stored dried and maintained uncovered. This speculation was once assumed in advance of setting up the suitable requirements for wound recovery materials. The pioneering paintings of wintry weather [28] designed the primary technology of wound movie or "dressings", the area he discovered that the epithelial repair of wounded pig pores and pores and skin was once as a minimum two times in comparison to the air-uncovered wounds.

Since this date, the studies and research on wound dressing development had been further heightened; suggesting ideal wound dressings want to hold a wetted environment with immoderate biocompatibility and restrict the bacterial contamination for accelerating the tissue regeneration. In the eighties, the wound dressings had been classified according to their wettability diploma into dried and moist dressings.

Table 1. The commercial hydrogel-based dressing is available on the market.

Commercial wound dressings	**Composition**	**References**
GranuGel^{R}	Hydrogel-based skin dressing that ensures a moist environment in necrotic wounds	[29]
ActivHeal^{V}	An amorphous hydrogel that keeps moisture in the injured site	[30]
NU-GEL^{TM}	Hydro-active hydrogel with calcium alginate. Keeps the injured area moist, helping to remove biological fluids	[31]
DermaSyn	Amorphous hydrogel dressing with vitamin E. Maintains moisture at the wound site, preventing tissue dryness.	[32]
CutimedV^{R} Gel	Amorphous hydrogel formed by Carbomer 940, purified water, glycerol, sodium hydroxide, and EDTA sodium	[33]
Purilon	Purilon-VR gel is made up of purified water, sodium carboxymethylcellulose, and calcium alginate.	[34]
INTRASITE^{R} Gel	A transparent hydrogel composed of carboxy-methylcellulose (CMC), propylene glycol, and water hydrates necrotic and flaky tissue and absorbs exudate.	[35]

Applications -

Hydrogels characterize a type of substance widely used in the gentle tissue engineering of skin, blood vessels, muscles and fats. Hydrogels are three-dimensional (3D) networks composed of physically or chemically cross-linked bonds of hydrophilic polymers. The insoluble hydrophilic structure provides excellent absorption capacity for wound exudate, allowing oxygen diffusion to accelerate healing.

Importantly, hydrogels have a highly hydrated 3D polymer community that can retain many times the dry weight of water, thus maintaining excess wound bed water levels. These unique physical properties allow hydrogel networks to be cast in a variety of sizes and shapes. Therefore, hydrogel-based substances are the most suitable dressings for covering pores and blemishes on the skin. In addition, hydrogels provide a platform for loading cells, antibacterial agents, growth factors, and various additives and biopolymers. In terms of resembling ECM, the hydrogel used in the wound healing application provides a 3D cell-friendly environment that promotes tissue regeneration with or without the presence of cells embedded in the scaffold.

Importantly, all hydrogels must meet the basic requirements for biocompatibility in scientific use, as well as the unique physical and mechanical properties that are optimal for pore and skin wound function. In addition, they must also provide an excellent microenvironment for blood vessel internal growth and cell proliferation [36, 37].

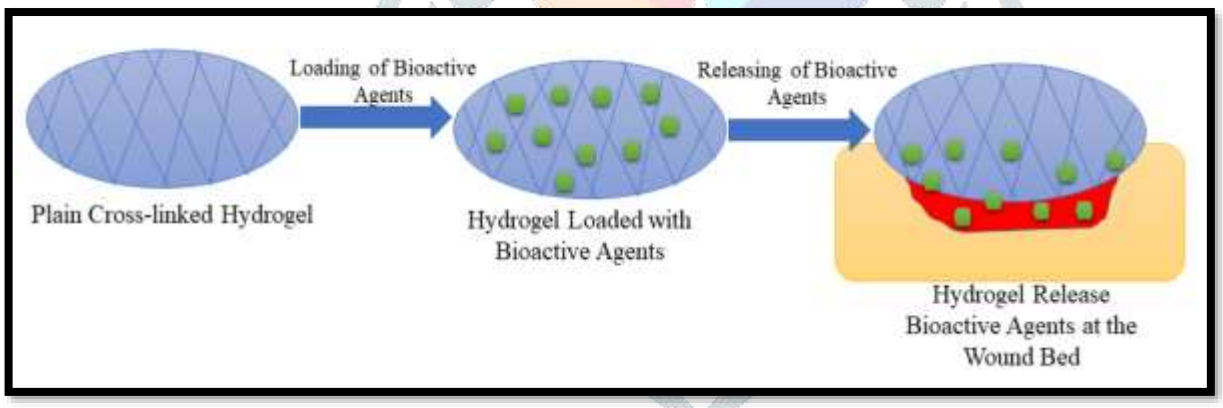

Figure 2: Cross-linked hydrogel loaded with bioactive agents.

Chitosan [38]:

Chitosan is a biodegradable polymer received from the deacetylation of chitinand can be cross-linked physically or chemically. Their amino and hydroxyl businesses 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).

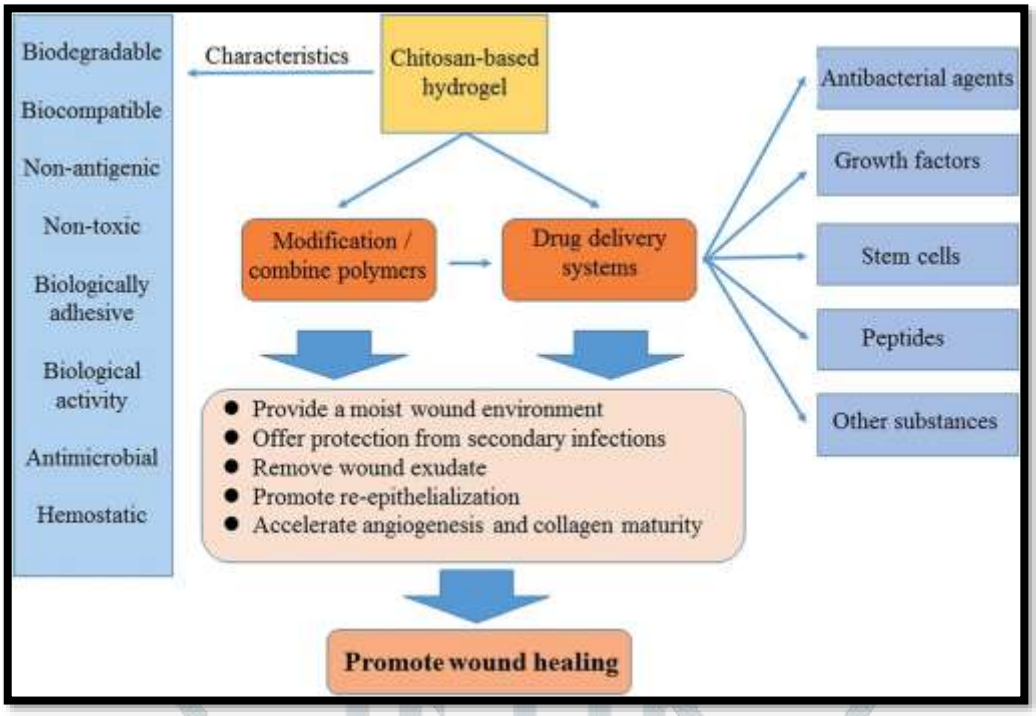

Figure 3: Application of chitosan-based hydrogel dressings.

Polyethylene glycol (PEG) [39, 40]:

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 by way of 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. 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.

Alginate [41]-

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-organisms (Staphylococcus aureus). The in vitro assay verified the nontoxicity of the material.

Gelatin [42]-

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. Confirmed a new kind of hydrogel primarily based on poly(glutamic 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 pore and skin dressing.

Cellulose [43]-

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). 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) Synthesize a multifunctional hydrogel primarily based on PVA/TEMPO-oxidized cellulose nanofiber intercalated with curcumin (TOCN-PVA-Cur). The results showed that the extent of 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) [44]-

In its chemical structure, carboxymethyl cellulose is a cellulose derivative that partially modifies the hydroxyl group with the help of carboxymethyl. In addition, because CMC is a biodegradable, biocompatible, non-

toxic, and hydrophilic material, it has interesting properties for application in the manufacture of dressings. A new type of hydrogel membrane has been synthesized for skin dressing applications. First, the material was developed using only carboxymethyl and then combined once with polyethylene glycol (PEG). Analysis showed that the material was once able to absorb significant amounts of liquid in the range of 100% to 5000%, confirming adequate cell viability. In addition, structural results purchased via FTIR revealed that the hydrogel contained a hybrid structure (amorphous form of CMC and semi-crystalline structure of PEG), confirming the cross-linking process.

Table 2: Characteristics, effects and applications of hydrogels

Types of hydrogels	Basic material	Hydrogel effect/property	References
Hydrogels containing Antibiotics	Polyethylene glycol (PEG)	Tetracycline could inhibit bacterial growth within 48 h and induce the formation of zones of inhibition on the agar plate.	[45]
	Keratin hydrogels	Burns treated with ciprofloxacin- keratin hydrogels Contained significantly less Pseudomonas aeruginosa and Staphylococcus aureus	[46]
	Polyvinyl alcohol-gelatin (PVA)	Natural debridement by hydrating necrotic tissue with loosening and absorbing slough and exudate in wounds. It also encourages autolytic debridement	[47]
Hydrogels used for the delivery of stem cells	Adipose Extracellular Matrix (ECM), Methylcellulose (MC)	Accelerated wound closure, re-epithelialization, neovascularization	[48]
	Collagen-Polyethylene glycol, fibrin	Less wound contraction Dermal matrix deposition	[49]
	Pullulan collagen	Accelerated wound closure, improve cell recruitment and functionality, neovascularization	[50]

	Pluronic F127	Angiogenesis resulted from the cells in the hydrogel cell proliferation, accelerated wound closure, regeneration of granulation tissue	[51]
	Chitosan and gelatin	Faster cell migration at the wound site, angiogenesis, higher capillary density	[52]
Smart hydrogels stimuli-responsive hydrogels	Aldehyde hyaluronic acid (A-HA)	pH- and HAase-dependent degradability that enables the release of more aminoglycosides-SS for on-demand and sustained anti-infection and antioxidant activity	[53]
	Sodium alginate/poly (N-vinyl caprolactam)	Temperature-pH dual responsive hydrogel with excellent free radical scavenging, anti inflammatory, antibacterial effect	[54]
	Alginate/polyacrylamide 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	[55]
	Sodium alginate/bioglass composite hydrogel	The hydrogel system sequentially delivers bioactive molecules for meeting the biological requirements and timeline of each wound healing stage	[56]
Hydrogels used for the delivery of bioactive agents	A mixture of polyvinyl acetate (PVA), gelatin and chitosan	Accelerated wound closure, re-epithelization; faster transition from the inflammatory to the maturation phase, enhanced collagen deposition, myofibroblasts, and vessel formation	[57, 58]
	Polyvinylpyrrolidone/polyethylene glycol-dimethacrylate (PVP/ PEG-DMA)	β-CDs immobilized in the PVP/PEG-DMA matrix stimulated a prolonged release of ibuprofen	[59, 60]

CONCLUSIONS-

Almost all of us have had to deal with an open wound in our lifetime. Most of these injuries were easily treated while others required medical attention. Wound management is one of the most important clinical areas because infected wounds can lead to serious complications. In this review, the authors aimed to conclude that current information on wound management and wound healing is primarily hydrogel-based. Hydrogel seems to be perfect to enhance ideal dressing, due to its many beneficial properties and versatility. The development of dressings suitable for all types of wounds remains elusive, and the secret to the successful treatment of injured patients lies in informing medical staff about the pathophysiology of the patient's pathology. wound and treatment possibilities. The development of new technologies and increased accessibility to clinical practice bring new therapeutic sources to patients, but their successful use requires pertinent information on the indications for treatment. treat. Recently, hydrogel dressings have become a convenient stand for wound care due to their flexible properties.

CONFLICTS OF INTEREST

There are no conflicts of interest and disclosures regarding the manuscript.

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