REVIEW ARTICLE

An Overview of Multiple Hydrogel Formulations for Wound Healing

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ABSTRACT

Wound healing is a complicated and active process involving four perfectly synchronized processes that compose the typical biological mechanism of wound healing in the body: hemostasis, inflammation, proliferation, and remodeling. In order to successfully healing of wounds, these four steps need to take place in the right order and timeframe. There are distinct types of wound healing, like acute and chronic wound healing, based on various conditions and causes. One or more steps of this operation may be impacted by a variety of variables, which may hinder or result in improper wound healing. The ideal wound dressing is crucial to heal the wound and keep it from getting infected again. Hydrogel is ideal because of its anti-inflammatory, microbiological, and readily available qualities. Numerous variables may interfere with or result in improper wound healing at one or more stages of this procedure. The appropriate wound dressing is crucial to heal the wound and prevent secondary infections. This page lists some of the numerous formulations where hydrogel is most suitable and frequently used now a day. This is because of its anti-inflammatory, microbiological, and easily accessible qualities.

Keywords: Acute wound, Applications of hydrogel formulations, Chronic wound, Hydrogel formulations, Phases of wound, Wound healing.

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INTRODUCTION

A crucial physiological process called cutaneous wound healing involves the association of various cell strains and their products.[1] In order for wound healing to occur as a regular biological process in body, it must pass through four stages: hemostasis, inflammation, proliferation, and remodeling. Various factors can prevent one or many phases of formation, which will affect how well or how slowly wounds heal. Features discuss containing infection, oxygenation, sex hormones, age, anxiety hyperglycemia, obesity, medicines, intoxication, smoking, and nutriment.[2] Wound healing occurs by involving the progressive activation of numerous types of cells and signaling paths in a sequenced manner.[3] It takes a complex interaction between many different cell types, including mediators, cytokines, and the vascular system for a wound to heal. Platelet aggregation and the first blood vessel constriction are scheduled in a certain order to limit bleeding. Starting with neutrophils, various kinds of the influx of inflammatory cell was followed and then release cytokines and mediators to encourage re-epithelialization, angiogenesis, and thrombosis at last fibroblasts serve as scaffolding.[4] Granulation tissue, neovascularization, and re-epithelialization are characteristics of the proliferative phase. This phase can last for some weeks.[5] Successful wound healing requires coordination between these stages, as well as proper nutrition and immune response Wound achieves tremendous strength as it grows during the maturation and remodeling period (Figure 1).[6]

Wound Healing Phases and Physiology

These stages are typically completed very fast in the case of acute wounds. Chronic wounds are characterized as those that persist signs of delayed healing of wounds 12 weeks after their initial trauma (Figure 2).

Hemostasis Phase

Vascular damage happens during surgical incisions on the micro or macrovascular level. The body's first reaction is to stop exsanguination and encourage hemostasis. In the layer of the vessel wall, increased intracellular calcium levels cause damaged arterial arteries to immediately constrict by constriction of smooth muscle. A transversal plane vessel may entirely shut through a contraction if the wound occurs. The decreased flow of blood caused by constriction of arterioles causes tissue hypoxia and acidity in a short time. NO, Vasoactive metabolites and adenosine are produced more readily, resulting in reflex vasodilation and relaxation of arteries. Mast cell production of histamine causes an increase in vascular permeability and vasodilatation, which makes it

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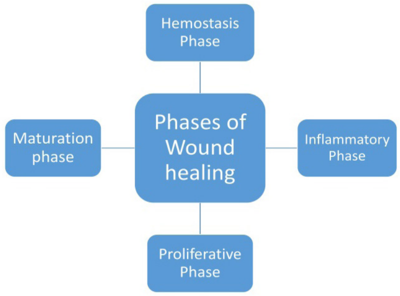

Figure 1: Stages of wound healing

easier for inflammatory cells to enter the extracellular region around the lesion. This explains why early wounds have a recognizable warm, red, swollen appearance.[7]

The development of a clot, which is accomplished through three main processes, also stops further loss of blood at this stage:

- *Intrinsic pathway*

Tissue injury causes endothelium damage, which allows blood to enter the sub-endothelial areas**,** which activates factor XII (Hageman factor) through the contact activation route of the intrinsic clotting cascade. As a result, factor X is activated, prothrombin is transformed into thrombin, fibrinogen is transformed into fibrin, and forming a fibrin plug.[8]

- *Extrinsic pathway*

Extrinsic coagulation system allows tissue factor, which the bulk of cells contain, to enter the bloodstream as a result of endothelial injury**.** As a result, factor VII and the remaining extrinsic pathway of the coagulation system are activated, leading to the activation of thrombin.[9]

- *Platelet activation*

After activation by ADP, thrombin or thromboxane Platelets alter the appearance and secrete the material. Activated platelets cling to exposed collagen sites to create a thrombocyte, plug and momentarily stop bleeding. Both filaments of actin and myosin found in platelets, as well as von Willebrand factor and fibrin, all contribute to the strength of this plug.[10]

Inflammatory phase

Infection prevention is the primary goal of this period. Neutrophils are the main defense against infection at the wound. To eliminate trash and bacteria, they primarily use three processes. It will firstly phagocytose, which is the direct absorption and removal of foreign materials. Secondly, there will be a degranulation of neutrophils and the discharge of several poisonous compounds that kill germs and dead host tissue. Additionally, neutrophils have the ability to produce "traps" of chromatin and proteases that can entrap and destroy bacteria in the extracellular environment. The action of neutrophil granulocytes stimulates the formation of oxygen-free radicals, which have been shown to have an antibacterial effect and, in interaction with chlorine, can disinfect a wound.[11]

Macrophages are phagocytic cells that are significantly bigger and reach their maximum number in wounds 48 to 72 hours after an injury. The abundance of growth factors in macrophages, such as EGF and TGF-β, is important for regulating the inflammatory responses, promoting angiogenesis, as well as boosting granulation tissue production.[12] Lymphocytes become visible inside the wound after 72 hours.

If it's necessary, this prevention phase of healing will continue, ensuring that all surplus germs and debris from the site are eliminated.[13]

Proliferative phase

Once the damaging stimulus is stopped, the proliferative phase of the wound healing cascade begins repairing the defect**.** Hemostasis is accomplished, the inflammatory reaction has been controlled, and the wound is free from debris. This multi-step process includes simultaneous angiogenesis, collagen deposition, the development of granulation tissue, epithelialization, and wound retraction.[14]

- *Angiogenesis*

When the hemostatic plug forms, platelets produce TGF-, PDGF, and the fibroblasts growth factor, which initiates angiogenesis. VEGF, produced in response to hypoxia and secreted with other cytokines, stimulates endothelial cells to encourage neovascularization and repair of blood vessel ruptures.[15] As the angiogenesis process progresses, healthy vessel outgrowths create a dense vascular network of capillaries that spreads throughout the wound. The capillaries are initially weak and porous to further exacerbate tissue edema and the emergence of healing granulation tissue.[16]

- *Fibroblast migration*

Growth factors emitted from the hemostatic clot encourage fibroblasts to proliferate and subsequently move to the wound. On day 3, the wound is colonized by fibroblasts that form collagen and fibronectin by depositing extracellular matrix protein.[17] When enough matrix has been deposited, fibroblasts transform into myofibroblasts and produce pseudopodia. This makes it possible for them to attach to nearby fibronectin and collagen proteins and aid in wound contraction. The main factor in giving strength to tissues is collagen produced by fibroblasts.[18]

- *Epithelialization*

Following early damage, epithelial cells proliferate along the ends of the incision till a thick layer of cells fully encircles the lesion and connects to the matrix. Epithelial cells acquire motility through an embryological procedure which is named epithelial-mesenchymal transition (EMT), which can move across the wound's surface. This stage could be completed in wounds that have largely healed within a day. To replenish epithelial cell levels and finish wound healing epithelial cells respond to changes in cytokine concentration by transitioning from a motile to a proliferative state.[19]

- *Wounds retraction*

Seven days after the initial damage, wounds start to close, primarily through the action of myofibroblasts. Actin and

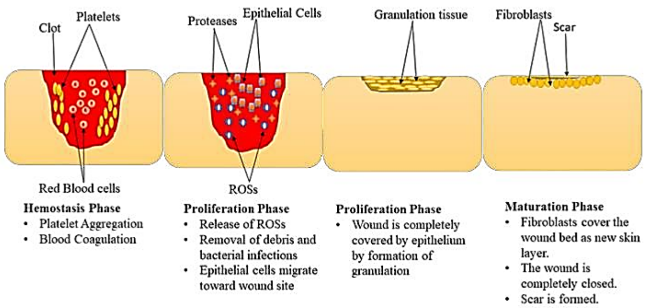

Figure 2: Different phases of wound healing physiology

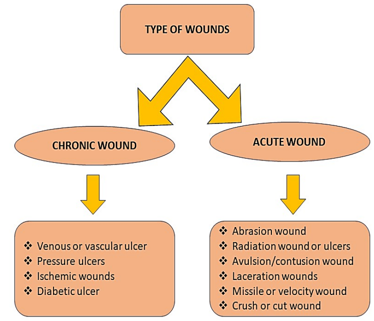

Figure 3: Types of wound

myosin interactions draw cell bodies close together, reducing the amount of tissue needed to repair. Shorter scars can result from contraction that happens at a pace of 0.75 mm each day. Numerous factors, including the geometry of the wound, affect how quickly it heals, with circular wounds healing more slowly than linear ones. Deformity and the development of contractures might result from disorders during this healing phase.[20]

- *Maturation phase*

It is also referred to as remodeling. The last stage of wound healing, Which might require two years, causes the injured tissue to stabilize and normal epithelial development. As collagen and some different proteins formed in the wound become more cohesive, this phase requires a balance between synthesis and breakdown. They will start developing a structure that resembles healthy tissue. Although, tissue strength in wounds is never the same, averaging just 80% over the long term and 50% of the initial tensile strength after three months. Vascularity reduces as the scar ages, and its color later shifted from red to pinkish to grey.[21]

Wound Healing Types

Our body's major organ, the skin, is a defensive barrier to keep us safe from pathogens and diseases. Skin breaks result in wounds. According to different sorts of circumstances, instances, and accidents, wounds are categorized as mild, moderate to severe, tiny to huge, superficial to deep, from burns, contusions, knife injuries, crushing injuries, needling injuries, to gunshot wounds, from acute to chronic wounds.[22,23] For instance, acute wounds, including minor abrasions, knife wounds, minor scalds, skin breaking, and the first stage of the wound following surgery occur rapidly and recover quickly. Venous lower extremity ulcers, arterial lower extremity ulcers, diabetic foot ulcers, chronic radiation exposure, and severe burns or scalds are examples of chronic wounds.[24-26] With substantially longer healing times.[23] Cleaning of the wounds is required to eliminate debris and contaminants, regardless of the type of injury or wound, and in the event of invading pathogens through the skin. To stop infection and inflammation, it's crucial to sterilize and cover the wound.[27,28] To avoid microbial contamination, certain infectious wounds, such as those caused by gunshots, typically require wound management (Figure 3).[29]

Chronic wound

Metabolic diseases cause chronic wounds. Contrary to acute wounds, which heal evenly as well as quickly, these wounds require an extended period to heal. Chronic wounds are out of equilibrium when synthesizing and decomposing cells and ECM, such as collagen. These lesions are often divided into three groups: diabetic ulcers, pressure ulcers, and venous/vascular ulcers. Ischemic wounds are a different class of chronic wounds that are also present (Figure 4).[30,31]

- *Venous or vascular ulcers*

Increased venous pressure brought on by venous reflux or blockage is known as venous hypertension. The primary underlying factor for ulcer development is assumed to be this process.[32]

- *Pressure ulcers*

localized damage to the skin or the tissues beneath the skin as a consequence of shear or pressure alone. Most PUs/PIs are related to pieces of equipment, usually a medical device., but they may also occur over a bony prominence.[33]

- *Ischemic wounds*

Ischemic Another kind of chronic wound is a wound that develops when the blood flow to the tissues is restricted, depriving the tissues of the oxygen and glucose needed for cellular metabolism.[34]

- *A diabetic ulcer*

Patients with diabetes experience wounds that exhibit slowed epithelization kinetics, protracted inflammation, and poor wound healing. Notably, 15% of T2DM patients experience the development of diabetic foot ulcers, which are localized sores on the lower limbs (DFUs). The most serious type of diabetic wound, DFUs has the potential to be fatal or require lower limb amputation.[35]

Acute wound

Different etiology and pathophysiology of acute wounds have an effect on how they develop naturally and how they should be managed. The typical healing time for acute wounds is six weeks after the trauma or inflammation that caused them. According to the types of environmental elements involved in the damage, acute wounds can be divided into a variety of categories.[36]

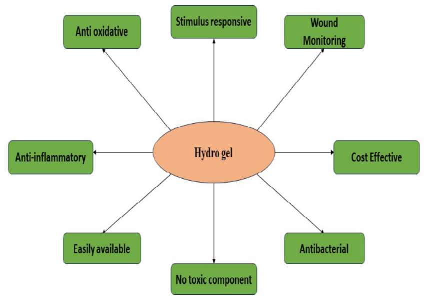

Figure 4: Properties of hydrogel

- *Abrasion wound*

Abrasions are wounds that tear the integrity of the tissue and harm the body's visceral linings as well as the skin.[37]

- *Radiation wounds or ulcers*

About 90–95% of people who receive therapeutic radiation experience it; it is the most common adverse effect of radiotherapy. The production of ROS, a decrease in the population of viable stem cells, the onset of dermal inflammatory reactions, and necrosis of skin cells caused radiation ulcer.[38]

- *Avulsion/Contusion wound*

These are traumatic injuries in which the skin's top layer is torn and a limited fraction of soft tissue covers the bones in the distal extremities.[39]

- *Laceration wound*

A laceration is a category of the wound in which the underlying tissues and skin are cut or damaged. Lacerations are a frequent occurrence for medical professionals. 13.8 million ER visits, or over 12% of all visits, were reported to be for laceration care in 2005.[40]

- *Missile or velocity wound*

Missile or Velocity wounds are induced when a bullet or another fast item penetrates the body, it causes injuries. Examples of missile wounds are ballistic injuries or gunshot wounds.[41,42]

- *Crush or cut wounds*

Injuries caused by high-energy trauma may result in fractures and bone deformities, necrosis, and damage to the skin and soft tissues, as well as damage to the nerves and blood vessels, called crush wounds (Table 1).[43]

An Ideal Treatment for a Wound

Wet dressings, as opposed to dry dressings, can expedite the healing of wounds. The only environment that may regenerate skin without causing inflammation or eschar formation is one that is moist.[49] It was decided that the wetted dressings would be good choices for wound treatment. An excellent wound dressing should have the qualities listed below: A few of the advantages include being nontoxic, able to relieve wound pain, and cost-effective. Others include controlling wound moisture, improving gas transport, removing excess exudates, preventing infections and bacteria, reducing wound surface necrosis, having mechanical protection, being easily changed and removed, and being elastic, biocompatible, and degradable.[50,51]

Applications of Hydrogel in Wound Healing

Hydrogels have been demonstrated to have enticing benefits in the realm of wound therapies due to their admirable biological and mechanical capabilities. The usage of hydrogel dressings is mostly due to their cutting-edge properties, including wound monitoring, antibacterial, adhesion and homeostasis, inflammation and anti-oxidation, substance delivery, self-transformation, stimulus-response, and cost-effectiveness.[52] Soft tissues like skin, blood vessels, muscle, and fat are typically created using a family of polymers called hydrogels.[53] Hydrogels are three-dimensional (3D) meshwork comprised of hydrophilic polymer linkages that have undergone mechanical or chemical cross-linking. The insoluble hydrophilic structures are remarkably good at absorbing injury discharges and facilitating oxygen scattering to accelerate curing.[54,55] In addition, hydrogels can bind far more substances due to their highly hydrated 3D polymer matrix. Because of their exclusive physical properties, hydrogel grids can be molded in a range of dimensions.[56,57] Hence, hydrogel-based dressings exist for treating skin wounds.[58,59]

Hydrogels Formulation in Wound Healing

In 2022, a patch with hydrogel electrode was designed to treat wound healing with fewer side effects and faster healing as electric stimulation increases healing with high efficacy and improves wound management. The patch showed antibacterial properties as the hydrogel is made up of two components methacrylate alginate and silver nanowire. In SD rats, the wound healed within 7 days because the patch stimulated the expression of growth factors by 'NIH 3T3'.[60]

Another formulation was developed in 2022 for the Wistar rat with type 1 diabetes because the rehabilitation process is delayed in diabetics due to the high glucose level and the increase in the formation of ROS, which delays the recovery of the epidermal barrier. Therefore, a formulation of the compound hydrogel was developed combining the hypolipidemic property of silk fibroin, the melanin property, and the medicinal effect of berberine to control oxidative stress, and the slow release of berberine provides a long residence time at the site of action and efficient migration of fibroblast cells. This formulation worked as a good wound healer as it provides support for the re-epithelization of tissue and encourages injury healing (Table 2).[61]

Free radical polymerization was used to make hydrogel membranes. In the incidence of the intruder ammonium peroxide sulfate (APS) and sodium hydrogen sulfite, the polymer PEG-4000 was cross-linked with the monomer 2-acrylamide-2-methylpropane sulfonic acid (AMPS) in an aqueous solution (SHS). N, N-Methylene-bis-acrylamide (MBA) was utilized as a cross-linker to create hydrogel membranes. Developed sheaths exhibited flexibility, were clear, and were spherical. The polymeric system was characterized

Table 1: Types of chronic wound with pathology and treatment

Types of chronic wound	*A pathophysiology*	*Treatment*
Diabetic foot ulcer	In diabetes, motor neuropathy affects muscles which leads to loss of sensation and awareness and actual ulceration. Macrovascular disease (atherosclerosis) can cause foot tissues to become ischemic, and while infection typically results from foot ulceration, it can also cause significant deterioration and delay in healing.	The use of antibiotics to treat infection Improvement of blood-glucose control will decrease microvascular complications. Routine surveillance will detect patients whose feet are at risk. [44]
Chronic radiation	Chronic radiation refers to the long-term effects of exposure to ionizing radiation, which can cause damage to the body's tissues and organs. Chronic radiation exposure can occur through a variety of sources, including medical procedures (such as radiation therapy), occupational exposure (such as nuclear power plant workers), and environmental exposure (such as living near a nuclear testing site)	Intensity-modulated radiation therapy (IMRT) reduces the complication Hold inhibitors like BRAF and MEK for 3 or more days before and after fractionated radiotherapy Supplementation with antioxidants to enhance immunity. [45]
Arterial lower extremity ulcer	Arterial insufficiency occurs because of atherosclerosis & refers to an injury in the arterial blood which leads to ischemia of tissue and cell death. This can occur both acutely & chronically and results in the development of ulcers.	Gentle cleaning Control of pain Occlusive uses of dressings Circulation improvement.[46]
Venous lower extremity ulcer	In addition to the inflammatory process and rising hydrostatic pressure, venous reflux and/or blockage can increase ambulatory venous pressures, which can eventually lead to the clinical signs of chronic venous sickness. The seriousness of the venous illness and the onset of symptoms that frequently proceed to ulceration are linked with venous system dysfunction, whether the profound or superficial system or both. Overload in volume and pressure causes valves to gradually fail.	Dressing of wounds in surrounding tissue like foam, and hydrogel. By compression therapy to control edema, Venous treatment Arterial revascularization.[47]
Knife wound	As the knife passes the tissue the increased velocity causes more damage. Permanent cavitation occurs in the space left by the tissue damaged by the piercing object, which forms a cavity.	Use of DPL and FAST can be performed to evaluate the steady patient with a knife/ gunshot wound Use of moisturizing cream Antifungal medicine Liquid Bandage. [48]

using FTIR, TGA/DSC, and SEM. Additionally, the effects of swelling, preparation loading, and delivering patterns at pH levels 5.4 and 7.5, irritant studies, *ex-vivo* medication -penetration, and accumulation studies were assessed. [72]

Numerous biological pathways and chemical reactions must be engaged and coordinated to restore tissue integrity during wound healing. The process of restoring the epidermal barrier through the production of new tissue is quite effective under normal physiological conditions. However, the natural healing process is slowed down in diabetic patients due to increased reactive oxygen species (ROS) production, pathogenic microbial attack, and high glucose levels. Effective methods for managing oxidative damage, promoting blood vessel growth, re-epithelialization, and collagen accumulation are necessary for the successful action of diabetic injuries. This study combines the hypolipidemic properties of silk fibroin (SF), melanin's antioxidant properties, and berberine's therapeutic impact to make a composite hydrogel for quick wound healing in diabetic conditions. Studies have shown that the hydrogel matrix's cross-linked mesoporous morphology allows for the steady release of berberine to deliver long-lasting therapeutic effects at the site of the wound. Under *in-vitro* circumstances, the composite hydrogel formulation controls oxidative stress, encourages efficient fibroblast cell migration, and is biocompatible. In a diabetic type I model of Wistar rat, the hydrogel encouraged wound repair and acted as a scaffold for tissue re-epithelialization. This study shows the efficacy of SF-melanin composite hydrogel with berberine as a possible bandage product for diabetic wound curing.[73]

An important aspect of chronic inflammation is macrophage (Ms) extraordinary flexibility. Therefore, a proper and timely shift from pro-inflammatory (M1) to anti-inflammatory (M2) Ms is essential through wound curing to encourage the determination of acute swelling and improve tissue patch-up. Exosomes from M2-Ms (M2-Exos), which are used in this study as confined microenvironmental signals to drive the reprogramming of M1-Ms toward M2-Ms for efficient wound supervision, contain putative critical regulators thought to be responsible for M polarisation. The hydrogels' breakdown time can be altered from 6 to 27 days by adjusting the tightness and cross-linking density. In an animal model for cutaneous wound healing, the localization of M2-Exos results in an efficacious local change from M1-Ms to M2-Ms within the lesion for more than 6 days, followed by improved therapeutic effects such as quick wound closure and improved healing quality. The hydrolytically degradable PEG hydrogel-based

Table 2: Formulations of curcumin for wound dressing

Sl. No	*Different Topical Formulation*	*Composition*	*Preparation Route*	*Observation*
1	Bandage (Polymeric)	Oleic acid, Chitosan c urcumin, Alginate,	Cross-linking and Ionic interaction	For 10 days, there was a let go of more than 40% of curcumin. Control, empty bandage, and curcumin bandage-treated injuries respectively reduce by 70, 80, and 94% after application on the 10^{th} day.[62]
2	Collagen film	Curcumin, Bovine collagen	Cross-linking	More than 60% of the curcumin was released, according to the *in-vitro* release kinetics, after 12 days of research. The administration of collagen films accommodates curcumin resulting in an exorbition assertion of collagen and the creation of granulation tissue.[63]
3	Methoxy poly (ethylene glycol)-graft-chitosan composite film containing curcumin nano formulation.	Curcumin, poly (e-caprolactone)-poly (ethylene glycol) methyl ether (MPEG-PCL) copolymer, linoleic acid, Tween1 20, chitosan	Casting/solvent evaporation method	8.4% of curcumin that was liberated early on the 1st day was released steadily over the succeeding five days. Once the wound area was less than 10% on day 14, an *in-vivo* wound curing examined fast recovery. On application, collagen's deposition wound healing, and fast re-epithelialization was all visible. [64]
4	Hydrogel nanocomposite	MPEG-PCL copolymer, oxidized alginate, chitosan, curcumin	Method of thin-film evaporation.	The hydrogel nanocomposite controls and tolerates the release outline of curcumin. On day 14, an *in-vivo* inspection presented that the wound had fully cured, enhanced collagen deposition, reepithelization, and granulation tissue growth. [65]
5	A liposome, a nanovesicle, and hyalurosome	Sodium hyaluronate, soy phosphatidylcholine, curcumin, and an ultrasonic disintegrator	Sonication	Biocompatible ingredients protected human keratinocytes from oxidative pressure injury *in-vitro*. When associated with further sets, *in-vivo* findings demonstrated better skin repair action in terms of reduced edema, myeloperoxidase activity, and initial skin re-epithelization. [66]
6	Gel-core hyaluronate (nanovesicle)	Hyaluronic acid, curcumin, Lipoid1 S100, and Tween1 80	Curcumin, Lipoid1 S100, Tween1 80, hyaluronic acid	Following a two-hour *in-vitro* investigation, there is a 50% release of curcumin. On day 10, the wound was cured with no scars when connected to other sets, with better granulation tissue development, collagen fiber deposition, re-epithelization, and tissue rejuvenation. [67]
7	Polymeric bio-adhesive emulsion	Neem and turmeric extract, shellac, casein, polyvinyl alcohol, and the maleic anhydride	Emulsion method	It has bacterial functions and is biodegradable and harmless. [68]
8	Hydrogel system containing micellar curcumin	PEG-PCL micellar curcumin, PEG-PCL-PEG copolymer hydrogel	Curcumin micelle by solid dispersion method and hydrogel by cross-linked methods	Enlarged collagen content, better granulation, and better wound development were all seen in the wound dressing study. Curcumin sustained 60% release over a lengthy 14-day period. [69]
9	Nanovesicles	Oramix1, Lipoid1 S75, PEG400, and curcumin	Sonication procedure	It is minute, sphere-shaped, multi-, or oligolamellar, and biocompatible. Less oxidative inflammation was observed after application to the skin inactivated by tissue plasminogen activator (TPA). Histology data exposed thick epidermis in numerous layers along with considerable re-epithelization. [70]
10	Curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles	Curcumin, poly (lactic-glycolic acid), polyvinyl alcohol	Technique for solvent evaporation in an oil/water emulsion	Over an 8-day period, there was a stable proclamation of curcumin, ranging from 40% to 75%. The PLGA's lactate release hastened angiogenesis and wound healing. According to histology and RT-PCR investigations, PLGA-curcumin demonstrated better re-epithelialization, granulation tissue development, and inflammation capability.[71]

exosome delivery technique could be used as a tool to control the local polarisation state of Ms, which is essential for tissue homeostasis and wound healing.[74]

There are two different types of bio-inspired adhesives for wound curing: chemical-rationale adhesives (like injectable hydrogels inspired by mussels) and physical-rationale adhesives (like octopus-inspired adhesive patches). Such compositions could take the place of common surgical wound dressings and tissue adhesives. As common materials like cotton fabric and gauze frequently absorb blood to produce a solid compound that causes additional bleeding and discomfort when removed. Even though medical closures can effectively close wounds, there may be additional harm from mechanical closure, necessitating removal.[75]

Burns are the most prevalent and deadly type of wound. They frequently come with irregular swelling, insufficient production of extracellular matrix, decreased angiogenesis, and an absence of development factor inspiration, all these aspects can cause complications and knowingly slow down the healing process. Chinese traditional medicine has employed pearl powder to indulge in wound healing. In the current investigation, we discovered that pearl peptides with a size range of ">10kd" that was supercritical CO_2 extracted have a great deal of possibility to accelerate wound healing at the cellular stage. Utilizing block-functionalized PEG/PPG polymers containing selenium, antioxidant hydrogels were created. Polymeric polymers containing pearl peptide components were created to create brand-new, promising wound dressings. It was demonstrated that pearl peptide hydrogels improved cellular resilience to oxidative stress, accelerated tissue remodeling, and encouraged increased wound healing and angiogenesis stimulation.[76]

Keratin, a bio-sourced polymer with a high sulfur content that is found in feathers, hair, hooves, horns, and wool, is the major component of these materials. Keratin-based formulations (KFs), which have high biocompatibility and inherent bioactivity, have generated a lot of academic interest. Abundant uses, like tissue manufacturing, drug delivery, and wound healing, have made extensive use of KFs. Along with pure KFs, mixed systems of keratin and other (bio) polymers have garnered significant attention as innovative keratinous formulations recently.[77]

By incorporating extracts of aloe vera mucilage (AVM) phytochemicals into the self-assembled polymeric group of two different silk fibroin (SF) proteins, we were able to create a photo-hydrogel without the need for chemical cross-linkers (from *Bombyxmori* and *Antheraea assamensis*). Additionally, the compound (SAP; comprised of SF, AVM, and PVP) hydrogel has been stabilized with polyvinylpyrrolidone (PVP), which also helped to give it its mucoadhesive properties. The hydrogel's physicochemical characteristics were assessed and contrasted with those of an SF hydrogel made entirely of SF proteins. The hydrogel's biocompatibility assessment in vitro revealed better proliferative and migratory responses, suggesting quicker hydrogel tissue repairability. A thorough in vivo comparison with the marketed product DuoDERM® gel showed that SAP hydrogel encouraged wound healing with improved extracellular matrix synthesis and remodeling. Additionally, the hydrogel showed its capacity to upregulate anti-inflammatory markers (IL-10, TGF-) and downregulate pro-inflammatory indicators (IL-1, TNF-) at the initial stages of recovery. Consequently, the combination of bioactive proteins and carbohydrates effectively accelerates skin regeneration and has significant conversion potential.[78]

Ginseng and sodium alginate nano hydrogel formulation was formulated, and rats were treated with surgically excised wounds, which increased dermal integrity, decreased reduced oxidative stress and inflammation, and increased the amount quantity of collagen deposition. This formulation increased the wound-healing properties of ginseng.[79]

A hydrophobic block polymer and the constituent of pearl polypeptide interacted to create a multifunctional thermal gel system with efficient wound healing regulation. The temperature-sensitive hydrogel can control the slow-release effect of pearl peptides, increase the pearl peptides' solubility and wound-healing activity, and significantly improve wound-healing activity. Thermal gels and pearl peptides have antioxidant activity, inhibiting the scavenging of unusually produced free radical molecules. [80]

2017 saw the development of a hydrogel that uses honey for its antibacterial and wound-healing qualities. Three honey concentrations were joined with chitosan and Carbopol 934 to generate topical honey hydrogel combinations. *In-vitro* release, pH, spreadability, swelling index, and antibacterial activity were all assessed for developed formulas. Spreadability was from 5.8 to 8.6 cm, while pH ranged from 4.3 to 6.8. Chitosan-based hydrogel showed increased *in-vitro* honey release with a diffusional exponent 'n' of 0.5, which indicates a Fickian diffusion process. Hydrogel formulations were tested for *in-vitro* antimicrobial efficacy against the bacteria that frequently cause burn infections, including *Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumonia, and Streptococcus pyogenes*, using the disc diffusion antibiotic sensitivity test. The hydrogel with the strongest antibacterial effect is 75% honey and 25% chitosan. Utilizing burn-produced injuries, *in-vivo* burn healing with this solution was examined in mice. In comparison to commercial products, the formula's burn healing and antibacterial properties were assessed. The hydrogel made of 75% honey and chitosan was shown to have the fastest rate of burn healing. According to the results of the current investigation, a hydrogel made of 75% honey and chitosan has better wound treatment action than commercial preparations and could be utilized as a safe and efficient natural topical wound treatment. [81]

A hydrogel was created utilizing in situ wound dressing to stop bleeding from wounds. This decreases inflammation and pain, which helps the wound heal more quickly. In addition to the two poloxamers (407 and 188), the matrix also contained a variety of other substances that had varying effects on the treatment. These substances included chitosan, which promotes wound healing by increasing its activity, aminocaproic acid, which stops wound bleeding, and povidone-iodine, which fights infections. This study demonstrated the effectiveness of hydrogel in accelerating wound healing, reducing hemostasis, and exhibiting significant bacteriostatic activity.[82]

CONCLUSION

The wound-healing process depends upon the type of dressing or dressing which can provide a sustainable environment for healing the wound. Hydrogels have been demonstrated to make certain enticing benefits in the area of wound care due to their improved biochemical and mechanical capabilities. Wounds are of different types and different physiology and need different treatments because of their mechanism. The subject of wound care is constantly expanding due to technological developments. While carefully using the patient's own tissues for rebuilding is still the best option available by providing protection against healing barriers, enhancing variables that promote wound healing, helping to bridge the gap between temporary and permanent restoration, and improving the outcomes of wound reconstruction, carefully planned reconstructive methods and novel products can aid in the ultimate healing process. Hydrogel shows one disadvantage its mechanical strength is poor the stability is very poor in swollen part of the wound. So, more research is needed to make hydrogel the ideal wound dressing. Hydrogel-based natural product outweighs when compared to synthetic ones. Current wound healing products and techniques increase a wound practitioner's toolkit for treating all aspects of wound care.

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