



Review Paper

Hydrogel-Based Topical Applications in Microbial Infection Control: A Comprehensive Review

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ABSTRACT

Because of their high moisture retention, biocompatibility, and capacity to distribute therapeutic agents directly to the afflicted area, hydrogel-based topical formulations have drawn a lot of attention for the treatment chronic wound infections. In order to improve wound healing and stop microbial growth, the current work focuses on the development and assessment of an antimicrobial hydrogel system. To enable continuous release at the wound site, the hydrogel was made using appropriate polymers and filled with an antibacterial medication. The efficacy of the formulation was evaluated using the variety of physicochemical and the biological tests, including the drug absorption, swelling behavior, antibacterial activity, and rheological analysis. The produced hydrogel shown excellent antibacterial activity and good Spreadability, stability, suggesting that it could be used to treat the infected wounds. Furthermore, the hydrogel's wet environment may promote the quicker tissue regeneration and lessen patient discomfort. Overall, the findings imply that the hydrogel is loaded with antimicrobial drugs that may be used in topically to treat the microbial infections as a safe and the efficient wound dressing.

INTRODUCTION

The largest organ in the body, human skin, acts as a remarkable protective barrier that divides the internal environment from the external surrounding. The skin, owing to its multifunctionality, is vital for moisturization, thermoregulation, sensory perception,

maintenance of humoral equilibrium, and protection against pathogens. Nonetheless, when this organ is subjected to external influences over an extended period, it can incur considerable strain. As a result, it may become vulnerable to numerous types of stimuli. When the skin's integrity is compromised, for example through wound formation, it can serve as a predisposing

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factor for various diseases.[1] Physical injuries that cause the skin to break or open are called wounds. To restore altered anatomical continuity and compromised functional status, wounds must heal properly. The epidermis. Restoring the integrity and functionality of injured tissues is the goal of the intricate process known as healing. Continuous interactions between cells and the matrix enable wound healing to occur in three overlapping phases: inflammation (3days), cellular proliferation (3–12 days), and remodeling (3–6 months). To restore the anatomical continuity and function of the afflicted part, the fundamental idea behind optimum wound healing is to limit tissue damage and provide sufficient tissue perfusion and oxygenation, appropriate nutrition, and a moist wound healing environment.[2]

Hydrogels are polymeric networks arranged in three dimensions that can take up water without disintegrating. Hydrogels have been investigated for important uses in wound healing, drug delivery, water purification, tissue engineering, scaffolding, and 3D printing. Hydrogels are characterized by a high surface-area-to-volume ratio, which enables rapid response and optimal interaction with the surrounding tissue. This is their main advantages.[3]

Hydrogels are classified into two categories based on the nature of bonding within the network: physical and chemical. When a crosslinker is added, it leads to the formation of covalent bonds between the polymer chains, resulting in the creation of a chemical hydrogel. On the other hand, a physical hydrogel arises when the polymer chains bond through hydrogen interactions, ionic forces, or other physical mechanisms. Hydrogels that are physically crosslinked do not necessitate a chemical crosslinker and are simpler to synthesize. However, they are easier to disturb than chemically crosslinked hydrogels.[4] Current methods for treating wounds encompass covering patches, gels, natural remedies like turmeric and

aloe vera, sutures, and medications. Nonetheless, each of these approaches has some limitations. Covering Patches serve solely to shield the wound site without offering any treatment. Natural remedies and medicines, such as gels, aid the healing process, but their effect is slow. Sutures are quite painful because they are direct and invasive. [5]

Physiology of Wound Healing

Depending on how long they take to heal, wounds are divided into two groups: acute and chronic. In general, a wound can be classified as chronic if it takes at least twelve weeks to heal. It can be classified as a wound that shows no evidence of healing, though, if the healing process takes longer than 30 days. Numerous internal and external factors influence the rate of healing. Reduced healing rates can be attributed to a number of reasons, including a shortage of extracellular matrix (ECM) proteins, increased production of reactive oxygen species (ROS), worsened swelling, hypoxia, decreased collagen formation, and attenuation of angiogenic growth factors. Chronic wounds include diabetic foot ulcers, pressure ulcers, and vascular ulcers. The wound's underlying protective epithelial layer has been damaged, making it useless. There is an ordered sequence of steps in the wound healing process. Slowdowns in this flow result in a cycle of inflammation, which makes the wound chronic. Increased ROS, chemokines, cytokines, and other chemicals correlated with inflammation are typically responsible for an increase in M1 macrophages and neutrophils at the chronic wound site. These cells also secrete matrix metalloproteinase (MMPs) molecules and reactive oxygen species (ROS), all of which contribute to inflammation. Scar tissues are the outcome.[6]

Wound Healing Phases:



The natural wound repair process, an essential physiological mechanism, requires the coordinated interactions of multiple cellular strains with their corresponding products. The skin's integrity needs to be maintained. To

properly steer the wound into complete healing succession, a complex biological healing process comprising hemostasis, inflammation, proliferation, and remodeling must be carried out.[7]

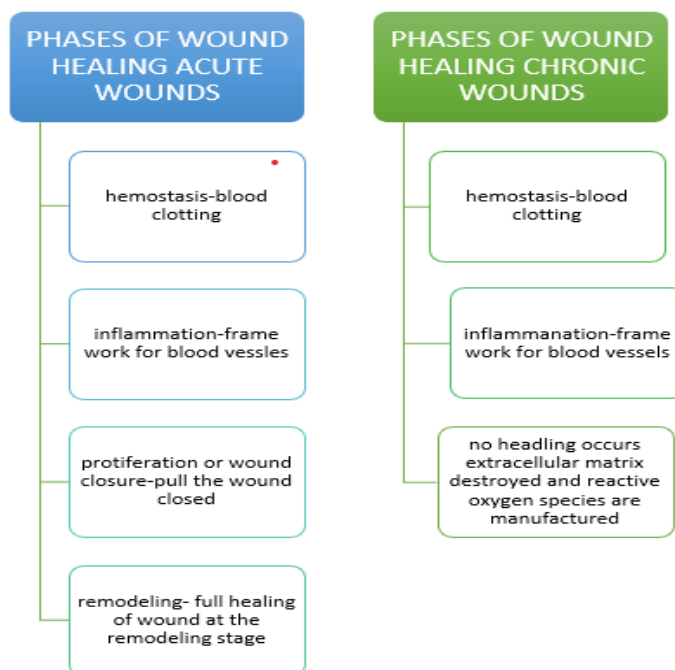


Figure 1: The four phases of wound healing

Molecular Mechanism Of Healing Process:

Coordinated cellular, humoral, and molecular mechanisms are involved in the intricate and dynamic process of wound healing, which starts as soon as an injury occurs and can last for months or years. Open or closed wounds can cause tissues to become impaired structurally and functionally. Regeneration or repair—the latter leading to fibrosis and scar formation—are the two ways that healing happens. This process resembles a coordinated interaction between growth factors, cytokines, and cells. Compensatory mechanisms permit healing to proceed even in the absence of specific cells or mediators. Restoring skin integrity and avoiding infection and dehydration depend on effective wound healing. Hemostasis, inflammation, proliferation, and remodeling are the four overlapping phases of adult wound healing. While lymphocytes build up by day four

and begin to decrease after two weeks, macrophages and monocytes peak during the proliferative phase. The second week is when remodeling starts, and it might last for several months. In general, immune cell interactions and the wound microenvironment play a crucial role in controlling tissue repair.[8]

Pathophysiology of Antimicrobial Hydrogels:

1. Wound Environment and Infection Risk-Open wounds

compromise the skin's protective barrier, exposing underlying tissues to microbial invasion. The wound bed becomes a moist, nutrient-rich environment, which:

- Encourages bacterial colonization and biofilm formation.
- Triggers chronic inflammation due to elevated levels of:

- Reactive oxygen species (ROS): Damaging to cells and ECM.
- Proteases: Degrade structural proteins like collagen.
- Cytokines: Sustain inflammatory cycles, delaying healing.
- Leads to impaired angiogenesis, hypoxia, and reduced ECM deposition, especially in chronic wounds like diabetic ulcers or pressure sores.[9]

2. Hydrogel Integration with Wound Physiology:

Hydrogels are 3D polymeric networks that resemble the extracellular matrix (ECM), offering:

- Moisture retention: Prevents desiccation and supports cell viability.
- Gas exchange: Allows oxygen diffusion, essential for healing.
- Cell migration and proliferation: Facilitates fibroblast and keratinocyte movement.
- Angiogenesis: Promotes new blood vessel formation.
- Nutrient diffusion: Supports metabolic activity of regenerating tissue.
- However, the hydrated environment can also promote microbial growth. Thus, antimicrobial functionality is critical to prevent infection while supporting regeneration.[10]

3. Release of Antimicrobial Agents in hydrogels

Hydrogels' high-water content, adjustable structure, biocompatibility, and capacity for both

prolonged and localized release make them ideal antimicrobial agent delivery vehicles. The hydrogel's polymer network, crosslink density, stimuli-responsiveness, and the kind of antimicrobial agent used all affect the release behavior.

Mechanisms of Drug Release from Hydrogels:

a. Diffusion-Controlled Release:

Most antimicrobial release occurs by diffusion, where drugs migrate through the water-filled pores of the hydrogel network. Diffusion depends on mesh size, swelling behavior, and drug molecular weight. Nanoparticle-loaded hydrogels (e.g., AgNPs, ZnO) especially rely on diffusion and slow ionic release for antibacterial effects.[11]

b. Swelling-Controlled Release:

Hydrogels that swell upon absorbing wound exudate increase pore size, enhancing antimicrobial release. Hydrophilic polymers such as alginate, gelatin, or chitosan exhibit significant swelling, making them suitable for topical wound applications.[12]

c. Degradation-Controlled Release:

Biodegradable hydrogels release antimicrobial agents as the polymer matrix undergoes enzymatic or hydrolytic degradation. In infected wounds, enzyme-responsive hydrogels degrade faster due to elevated protease levels, enhancing release.[13]

4. biofilm disruption:[14]

Table 1 : Biofilm Disruption Mechanisms of Antimicrobial Hydrogels.[14]

Mechanism	Description	How Hydrogels Facilitate This Mechanism
1.Enzymatic Degradation of Biofilm Matrix	Enzymes (e.g.,DNase, proteases, dispersin B) break down extracellular polymeric substances (EPS) of biofilms.	Hydrogels load enzymes and release them locally at the infection site to degrade EPS and weaken biofilm structure.



2. Reactive Oxygen Species (ROS) Generation	ROS such as $\bullet\text{OH}$, H_2O_2 , and O_2^- cause oxidative damage to bacteria and EPS.	ROS-generating hydrogels (e.g., metal oxide-based) continuously or stimuli-responsively release ROS at the wound site.
3. pH-Responsive Disruption	Many biofilms acidify their environment; acidic pH destabilizes certain hydrogel matrices to release antimicrobials.	pH-responsive hydrogels swell or degrade in low pH to release antibiotics, AMPs, or nanoparticles that destroy biofilm bacteria.
4. Chelation of Divalent Ions ($\text{Ca}^{2+}/\text{Mg}^{2+}$)	Removing Ca^{2+} and Mg^{2+} ions disrupt cross-linking stability within EPS.	Hydrogels incorporating chelators (e.g., EDTA) release them to destabilize biofilm ionic bridges.
5. Mechanical Disruption (Swelling Pressure)	Physical expansion exerts force on biofilm clusters, breaking them apart.	Super-swelling hydrogels absorb exudates and swell, causing mechanical detachment of biofilm layers from tissue.
6. Nanoparticle-Mediated Disruption	Metal nanoparticles (Ag, ZnO, CuO) penetrate biofilms, generating ROS and damaging membranes.	Hydrogels provide a controlled-release platform for sustained delivery and deep penetration of nanoparticles into biofilms.
7. Antimicrobial Peptide (AMP) Action	AMPs disrupt bacterial cell membranes and destabilize biofilm structure.	AMPs are embedded in hydrogels and released gradually to inhibit bacterial adhesion, aggregation, and biofilm development.
8. Quorum Sensing Inhibition	Interferes with bacterial communication pathways, preventing biofilm maturation.	Hydrogels deliver quorum-quenching molecules (e.g., furanones, RNA analogs) directly to infection sites.
9. Localized Heat/Photothermal Disruption	Heat damages EPS and bacterial membranes, enhancing drug penetration.	Photothermal hydrogels containing nanoparticles (e.g., gold nanorods) generate heat upon light exposure to destroy biofilms.
10. Targeted Drug Release Through Biofilm Stimuli	Biofilms produce enzymes (e.g., gelatinases), lowering O_2 and changing redox potential.	Stimuli-responsive hydrogels release drugs only in the presence of biofilm-specific signals, enhancing penetration and killing efficiency.

5. Biofilm Disruption

Biofilms are structured bacterial communities encased in extracellular polymeric substances (EPS), highly resistant to antibiotics. Antimicrobial hydrogels disrupt biofilms through:

- Enzymatic degradation: DNase, proteases, dispersion B break down EPS.
- Chelation of stabilizing ions: Removes $\text{Ca}^{2+}/\text{Mg}^{2+}$ to destabilize biofilm matrix.
- Mechanical biofilm layers.
- infiltrate biofilms and generate ROS.

- Stimuli-responsive release: Hydrogels release drugs in response to biofilm-specific signals (e.g., acidic pH, enzymes).[15]

6. Host Response and Healing Enhancement

By reducing microbial burden and inflammation, antimicrobial hydrogels positively influence the wound healing cascade:

- Lower neutrophil and M1 macrophage infiltration: Reduces pro-inflammatory signals.
- Promote M2 macrophage polarization: Encourages tissue repair and angiogenesis.

- Enhance fibroblast activity: Boosts collagen synthesis and ECM remodeling.
- Accelerate re-epithelialization: Supports keratinocyte migration and skin barrier restoration.
- Minimize scarring: Controlled healing reduces fibrosis and improves cosmetic outcomes.[16]

Factors affecting wound healing process. [17]

- Growth factors, extracellular matrix, blood components, and cytokines interact
- Cytokine-mediated basement membrane formation
- Prevention of dehydration
- Promotion of inflammation and granulation tissue formation
- Local factors (hypothermia, pain, infection, radiation, low tissue oxygen)
- Systemic health conditions
- Inadequate nutrition
- Advanced age
- Protein deficiency
- Vitamin deficiency
- Mineral deficiency

Antimicrobial hydrogels

Hydrogels with antimicrobial properties are highly promising materials for application such as wound dressings and fillers. Gels offer a moist and heavily hydrated environment for the wound area, thanks to their high-water content. This environment promotes cellular immunological activity that is crucial for the wound healing process. Nonetheless, the same hydrated environment can also promote microbial infection.

Therefore, it is desirable for gels to have antimicrobial properties in addition to serving their primary functions (such as wound healing, drug delivery, etc.).[18]

It has been reported that metallic nanoparticles, such as those made of silver, gold, or copper, can eliminate various kinds of bacteria. Every one of these nano-metals possesses unique characteristics and operates through a distinct mechanism. It is suggested that the primary antimicrobial action of nanometals consists of interfering with metabolic processes in the cell membrane. Microbial mortality can occur when metallic nanoparticles permeate the cell membrane and disrupt related enzymes. Additionally, metal nanoparticles may produce reactive oxygen species (ROS), which can cause DNA damage and bacterial mortality. Bacterial replication is additionally impeded by nanoparticles attaching to the cell membrane. The size, shape, and concentration of antibacterial nanoparticles are important features. [19]

pH-Responsive hydrogel

It is known that pH can vary at multiple locations in the body, including the gastrointestinal tract, vagina, and blood vessels. These differences may provide a suitable basis for pH-responsive medication release. Additionally, local pH fluctuations in respect to specific substrates can be created and used to modify the release of drugs. The goal of pH-responsive drug delivery systems is to release pharmaceuticals intravascularly when blood pH is increased in certain cardiovascular abnormalities, mask the taste of bitter therapies, and provide peroral controlled administration of drugs.[20]



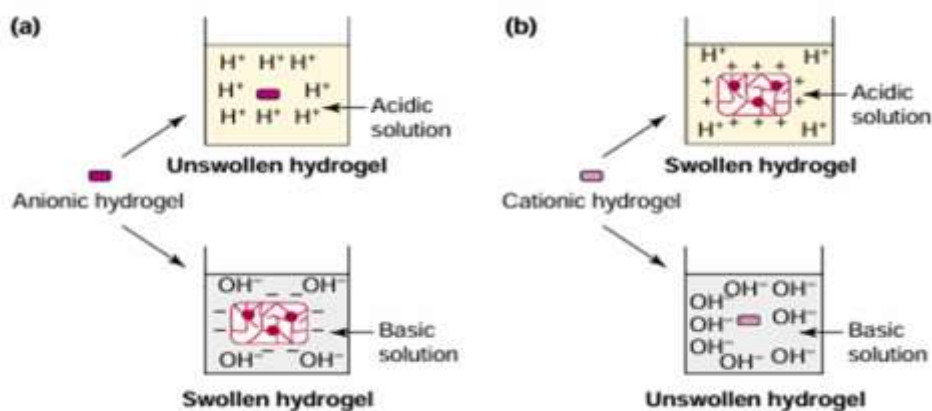


Figure 2: Swelling of (a) anionic and (b) cationic hydrogels in responses to pH

Thermosensitive hydrogels

Hydrogels that show temperature-sensitive behavior are referred to as thermosensitive hydrogels. Under low temperatures, these hydrogels stay in a sol form; however, when exposed to body temperature, they convert into a gel state. They can be used as an alternative to traditional wound dressings because of their special quality. Certain substances including β -glycerol phosphate, HPMC, and poloxamer can be added to chitosan to create a temperature-sensitive hydrogel. Odinokov. used Ter phthaloyl diazide to cross-link chitosan to create pH- and thermosensitive hydrogels. Bhattarai et al. created a hydrogel by neutralizing a chitosan solution with a polyol counter-ionic single-head salt. At low temperatures, this hydrogel stays liquid, but at body temperature, it solidifies into a gel. As therapeutic drug delivery methods for encouraging skin tissue regeneration and repair, these thermosensitive chitosan-based hydrogels show promise. They accomplish this by releasing loaded medications in a controlled and prolonged manner.[21]

Ideal properties of hydrogels to promote wound healing. [22]

➤ Healthy skin is composed of the epidermis, dermis, and subcutaneous layers, which protect the body from harmful attacks and give

the neurological and circulatory systems physical support.

- Significant water loss, decreased sensibility and thermoregulation, and bacterial infection result from the skin injury's breakdown of the protective layer.
- A number of macromolecules and cells control the intricate and dynamic process of wound healing in an orderly manner. Innate biological processes and environmental stimuli play a major role in the regeneration of skin, which acts as a barrier between the body and the outside world.
- As a result, hydrogel, which serves as a temporary skin substitute, would have certain qualities that would both offer physical protection and speed the healing of wounds.
- Similar to healthy skin, hydrogel may retain a moist environment by absorbing extra fluid. to support the skin.

Natural and Synthetic Hydrogel

Hydrogel wound dressings are developed using diverse natural and synthetic polymers. Natural polymers include chitosan, gelatin, hyaluronic acid, and alginate. Synthetic polymers include polyethylene glycol, polyvinyl pyrrolidone, polyethylene oxide, and polyvinyl alcohol. Hydrogels can be highly elastic, and this reduces mechanical power; therefore, multipolymeric

hydrogels have introduced for improved mechanical Hydrogel wound dressings are developed using diverse natural and synthetic polymers. Natural polymers include chitosan, gelatin, hyaluronic acid, and alginate. Synthetic polymers include polyethylene glycol, polyvinyl pyrrolidone, polyethylene oxide, and polyvinyl alcohol. Hydrogels can be highly elastic, and this reduces mechanical power; therefore, multi polymeric hydrogels have been introduced for improved mechanical power and absorption. Combining a naturally occurring polymer with a synthetic polymer promises to be a viable approach for generating materials with the desired thermal and mechanical attributes. Advancements in the field have been achieved by harnessing the inherent features of polymers, leading to the development of novel technologies such as

sprayable hydrogels, “smart hydrogels”, nanogels, aerogels, and cryogels.[23]

A. Natural hydrogels

Natural hydrogels are mainly made up of proteins and ECM components, making them inherently biocompatible and bioactive. Their capacity to boost various cellular functions suggests they could be a good fit for a range of biomedical uses. The composition and properties of these materials are similar to the intrinsic qualities of tissue layers. Nevertheless, they are subject to some limitations, mainly due to the challenges associated with their manipulation arising from variations observed between different batches. Hydrogel variants display distinct characteristics that make them more suitable for their intended use. A brief discussion of the different natural hydrogels will follow.[24]

Table 2: Natural Polymers. [25,26,27]

Polymer	Origin / Structure	Key Properties	Limitations	Applications / Notes
Chitosan.	Derived from chitin; polysaccharide of D-glucosamine & N-acetyl-D-glucosamine	Cationic, antibacterial, biocompatible; properties depend on molecular weight & deacetylation	Low mechanical strength; requires cross-linking	CMCS hydrogel: 132% swelling; accelerates diabetic wound healing
Hyaluronic Acid.	Glycosaminoglycan; N-acetyl glucosamine + glucuronic acid	Biocompatible, hydrophilic, biodegradable, non-immunogenic	Rapid degradation unless modified	Maintains moisture; widely used in wound healing
Gelatin.	Derived from collagen; rich in glycine, proline, hydroxyproline	Excellent cell adhesion, biocompatible, ECM-mimicking	Low mechanical strength; needs cross-linking	Used for tissue regeneration; crosslinked via EDC or glutaraldehyde

B. Synthetic Hydrogels

Due to their mechanical properties, ease of shaping into different configurations, and cost-effectiveness in manufacturing, synthetic polymers have shown significant efficacy in biomedical applications.[28] These polymers are stable and easy to use, but their biocompatibility is limited. Unlike their naturally occurring counterparts, synthetic polymers have the advantage of being able to be produced conveniently on an industrial scale. Moreover, due to their built-in adaptability, they can be used in different configurations that foster optimal tissue development. Furthermore, the capability to accurately control both the hydrophilic and

hydrophobic areas of synthetic polymers allows for the creation of frameworks that are more uniform as well as an enhanced ability to retain water. By combining them with biopolymers, hybrid polymers (blended) can be created that demonstrate advantageous physicochemical properties. Bioactive substances obtained from natural sources enhance the positive attributes of blended hydrogels made from synthetic polymers. Blended hydrogels offer a promising option for future wound treatment by integrating their beneficial properties. Examples of synthetic polymers are polyvinyl alcohol, polyethylene glycol, and polyvinyl pyrrolidone.[29]

Table 3: Synthetic Polymers. [30,32,33,]

Polymer	Structure / Nature	Key Properties	Limitations	Applications / Notes
Polyethylene Glycol (PEG)	Hydrophilic, ether-based polymer	Biocompatible, prevents protein adsorption, tunable (PEGDA/PEGDM)	Not bioactive unless functionalized	Used in diabetic wound dressings; reduces scarring
Polyvinyl Alcohol (PVA)	Hydrophilic, semi-crystalline polymer	Biocompatible, stable, moisture-permeable	Requires antibacterial enhancement	Double-crosslinked PVA/chitosan hydrogels improve rigidity & healing time
Polyvinyl Pyrrolidone (PVP)	Synthetic, lactam ring	Highly hydrophilic, good film-forming ability	Low mechanical strength alone	Used in blends with PEG/PVA
Polyethylene Oxide (PEO)	High molecular weight polyether	Highly soluble, flexible	Weak without crosslinking	Improves swelling and flexibility in blends

Table 4: Comparison Between Hydrogel Types in Terms of Biocompatibility and Effectiveness [34]

Hydrogel Type	Biocompatibility	Effectiveness
Natural Hydrogels (Alginate, Chitosan, Collagen, Gelatin)	<ul style="list-style-type: none"> • Highly biocompatible • Low toxicity • Good tissue compatibility 	<ul style="list-style-type: none"> • Excellent wound healing • Good moisture retention • Supports cell growth • Faster degradation • Lower mechanical strength

Synthetic Hydrogels (PVA, PEG, Pluronic, PMMA)	<ul style="list-style-type: none"> • Good biocompatibility • May need modification for cell affinity 	<ul style="list-style-type: none"> • Strong mechanical strength • Controlled drug release <ul style="list-style-type: none"> • High stability • Lower cell adhesion
Semi-Synthetic Hydrogels (GelMA, PEG-chitosan, Carbopol blends)	<ul style="list-style-type: none"> • Improved biocompatibility due to combination 	<ul style="list-style-type: none"> • Balanced strength and biodegradation <ul style="list-style-type: none"> • Tunable drug release • Suitable for antibiotics/growth factors
Smart/Stimuli-Responsive Hydrogels (pH-, temperature-, enzyme-responsive)	<ul style="list-style-type: none"> • Depends on polymer used 	<ul style="list-style-type: none"> • Targeted drug release • Responds to infection environment <ul style="list-style-type: none"> • High precision • Higher cost
Nanocomposite Hydrogels (AgNPs, ZnO, graphene)	<ul style="list-style-type: none"> • Biocompatibility varies • Nanoparticles may irritate at high dose 	<ul style="list-style-type: none"> • Strong antimicrobial activity <ul style="list-style-type: none"> • Enhanced strength • Better healing • Possible nanoparticle toxicity
Ionic-Crosslinked Hydrogels (Calcium alginate)	<ul style="list-style-type: none"> • Excellent biocompatibility 	<ul style="list-style-type: none"> • Good for rapid healing <ul style="list-style-type: none"> • High absorption • Lower mechanical strength
Covalently Crosslinked Hydrogels	<ul style="list-style-type: none"> • Good if non-toxic crosslinkers used 	<ul style="list-style-type: none"> • High stability <ul style="list-style-type: none"> • Long-term drug release • Possible toxicity if residues remain

Advantages.[35]

1. Hydrogel has more strength and elasticity.
2. Hydrogel is easily modifiable and has good transparency qualities.
3. They have a degree of flexibility that is quite similar to natural tissue because of their high water content.
4. They can be injected and are biodegradable and biocompatible.
5. Hydrogel can detect changes in pH, temperature, or metabolite concentration and release its load in response.
6. Timely release of nutrients or medications.

Applications

Table 5: Applications of hydrogel[36-38]

Application	Description
Wound Healing	Hydrogels have a cross-linked structure that allows them to hold large amounts of water and drugs. Their high water-holding capacity helps in absorbing and retaining wound exudates, thereby maintaining a moist environment favorable for healing. Polyvinyl pyrrolidone and polyacrylamide hydrogels typically contain 70–95% water.
Colon-Specific Hydrogels	Polysaccharide-based hydrogels are designed for colon-specific drug delivery due to the high concentration of polysaccharide-degrading enzymes present in the

	colon. Dextran hydrogels are commonly used for this purpose.
Drug Delivery in the Gastrointestinal Tract	Hydrogels enable site-specific drug delivery in the GIT. In the presence of intestinal microflora, colon-specific hydrogels exhibit tissue specificity. Variations in pH and enzymatic activity cause hydrogel degradation and controlled drug release.
Transdermal Drug Delivery	Hydrogel-based drug delivery systems are developed for transdermal administration. These formulations are also explored in iontophoresis to enhance the permeation of drugs such as hormones and nicotine through the skin.
Gene Delivery	Changes in hydrogel composition allow effective targeting and delivery of nucleic acids to specific cells for gene therapy. Hydrogels show strong potential in treating various genetic and acquired diseases.

Table 6: Methods of preparation of hydrogel.[39-43]

Method	Description
Free Radical Polymerization	Uses initiators (APS, UV light) to form polymer networks.
Ionic Crosslinking	Uses ions like Ca^{2+} to crosslink polymers (e.g., alginate).
Chemical Crosslinking	Uses covalent crosslinkers such as GA, EDC/NHS, Genipin.
Physical Crosslinking	Gelation via hydrogen bonding, crystallization, hydrophobic interactions.
Thermo-Responsive Gelation	Polymers gel upon heating/cooling (e.g., PNIPAM, Pluronic).
pH-Responsive Gelation	Gel formation triggered by specific pH levels.
Enzymatic Crosslinking	Uses enzymes like HRP or transglutaminase for gelation.
Radiation Crosslinking	Gamma/e-beam radiation induces polymer crosslinking.
Click Chemistry	Fast covalent bonding (Thiol-Ene, etc.).
Freeze-Thaw Method	Repeated freezing and thawing cycles (commonly for PVA).
Self-Assembly Method	Peptides or block copolymers self-assemble into gels.

Evaluation OF Hydrogel. [44-46]

➤ Physical appearance:

Visual observations were used to assess the produced gels' homogeneity and physical appearance. The commercial formulation served as the standard.

➤ Spread ability test:

Spread ability can be assessed by spreading the gel on a level surface and looking for any grit in the hydrogel. A 1% hydrogel formulation in deionized water was made, and the pH was measured.

➤ Drug content:

Diclofenac sodium was extracted from 1 g of each gel formulation using 20 mL of phosphate buffer pH7.4 for 30 minutes in order to test the drug in gels. A membrane filter with a pore size of 0.45 μm was used to filter the final combination. Following the proper dilution with phosphate buffer pH 7.4, the absorbance of the sample was measured spectrophotometrically at 276 nm using an Elico SL150 UV-VIS spectrophotometer. The calibration curve was used to quantify the diclofenac sodium concentration.

➤ Determination of viscosity:

The Brookfield viscometer with spindle number 7 was used to measure the viscosity of the gel compositions at 25 $^{\circ}\text{C}$ and 100 rpm.

➤ Accelerated stability studies:

The International Conference on Harmonization (ICH) requirements were followed when conducting stability studies on improved formulations. According to ICH guidelines, the formulation in an aluminum tube was put through three months of accelerated stability testing at a temperature of $40 \pm 2^\circ\text{C}$ and a relative humidity of $75 \pm 5\%$. Over the course of three months, samples were collected at regular intervals of one month and examined for changes in pH, spreadability, drug content, and in-vitro drug release using the previously described method. If there were any modifications in the evaluation criteria, these were recorded. Tests were conducted in duplicate, and the standard deviation and mean of the observed data were recorded.

FUTURE PROSPECTS

- Advancements will focus on smart, stimuli-responsive systems that release drugs only when infection occurs.
- Nanocomposite hydrogels with metal nanoparticles and enzymes will improve biofilm disruption and accelerate healing.
- Hybrid natural–synthetic hydrogels will offer better mechanical strength and controlled biodegradation.
- Hydrogels will also evolve as carriers for growth factors, genes, and regenerative molecules, promoting faster tissue repair.
- The integration of 3D bioprinting, wearable sensors, and personalized medicine will lead to next-generation intelligent wound dressings with real-time monitoring and targeted therapy.
- Especially for superficial microbial infections, Class II and Class III antimicrobial drugs such as Mupirocin, Fusidic acid, Clindamycin, Gentamicin, Metronidazole, Ciprofloxacin, Norfloxacin, Silver nanoparticles, and

Chitosan-based drugs can be incorporated into hydrogels to provide better therapeutic action.

- These drugs show strong antibacterial effects and can be released in a controlled and sustained manner, which helps in treating minor burns, cuts, skin infections, diabetic ulcers (initial stage), and pressure sores

CONCLUSION

Antimicrobial hydrogels have proven to be advanced wound dressing materials that not only protect the wound but also actively promote the healing process. Their three-dimensional structure maintains optimal moisture, supports cell migration, and enhances tissue regeneration while simultaneously delivering antimicrobial agents to prevent infection and biofilm formation. Stimuli-responsive hydrogels further improve treatment effectiveness by releasing drugs in response to changes in pH, temperature, or enzymatic activity within the wound environment. By combining the biocompatibility of natural polymers with the durability of synthetic materials, modern hydrogel systems offer improved mechanical strength, controlled drug release, and faster wound closure. These properties make antimicrobial hydrogels a promising and efficient alternative to conventional wound care approaches, especially for chronic and infected wounds.

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