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Review Article

Nanoparticles Reinforcing Hydrogels: A Novel Approach to Improving the Properties of Wound Healing Hydrogels

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Abstract

Hydrogels, which are porous three-dimensional polymers with a high capacity for water absorption, have a wide range of applications in biomedical engineering, particularly in wound healing. However, limitations such as low mechanical strength and the absence of controlled drug release hinder their effectiveness. Incorporating nanoparticles (NPs) into hydrogels presents an effective solution to enhance these properties. NPs not only serve as drug carriers, improving drug stability and enabling controlled release, but certain types, such as silver (Ag), gold, and silica NPs, also augment the anti-inflammatory and antibacterial properties of hydrogels. Additionally, metal NPs, including Ag, copper, and zinc oxide (ZnO), contribute to reducing the risk of infection and accelerating the wound healing process through mechanisms such as the production of reactive oxygen species (ROS) and the inhibition of microbial proliferation. Furthermore, the incorporation of nanomaterials, such as carbon nanotubes and silica v, enhances the strength, flexibility, and durability of hydrogels in physiological environments. These advancements have positioned nanoparticle-reinforced hydrogels as a promising option in the fields of regenerative medicine and tissue engineering.

Keywords: hydrogel, nanoparticles, wound healing

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1. Introduction

Currently, hydrogels are three-dimensional networks that have wide therapeutic applications due to their desirable properties. A variety of polymers are the main constituents of hydrogels. Through a process known as polymerization, one or several types of molecular building blocks so-called monomers are coming together covalently to form a much higher molecular weight material of homo or heteropolymer. Hydrogels are three-dimensional polymer networks made from natural or synthetic polymers that include an extensive range of structural forms and chemical compositions [1-7].

The basic characteristic of hydrogels is their ability to adsorb and maintain a lot of water through their hydrophilic functional moieties (e.g., carboxyl, hydroxyl, ether, and amino groups) groups [8-10]. Bemmelen was the first to use the term “hydrogel” to describe hydrophilic polymer systems with high efficiency for absorbing large amounts of water in their interstitial networks [11].

Different physical and chemical methods are used to form hydrogels. Physical hydrogels are obtained due to molecular entanglement and/or secondary forces such as ionic, hydrophobic, and hydrogen bonds. On the other hand, a chemical process, i.e., chemical covalent cross-linking (simultaneously or post-polymerization) is utilized to prepare a chemical hydrogel. Physical hydrogels are reversible due to conformational changes whereas chemical hydrogels are irreversible because of configurational changes. The double network hydrogels (interpenetrating networks) are formed by the combination of physical and chemical cross-linked hydrogels due to an electrostatic interaction between their moieties. The latter, recently has been employed to overcome the disadvantages of using a uniform physical or chemical hydrogel for example low liquid uptake capacity over changes in the pH [12].

The building blocks of hydrogels are artificial polymers, natural polymers, or a combination of both. Acrylic acid, poly (*N*-isopropyl acrylamide), poly (ethylene) glycol (PEG), and poly (vinyl alcohol) (PVA) are examples of synthetic polymers. Hydrogels fabricated in the presence of these polymeric structures possess advanced functional behavior and mechanical strength (strong gel integrity) compared to those fabricated naturally. On the other hand, the toxicity and bio-incompatible nature of synthetic polymers limit their use [13-17].

Unlike artificial hydrogels, natural hydrogels have recently attracted considerable attention because of their cost-effectiveness, desirable biocompatibility, and biodegradability [18]. Polysaccharides [alginate, cellulose, chitosan (CS)] and proteins (whey protein, soy protein, pea protein) are decent materials for the formation of natural hydrogels [19, 20].

Hydrogels also can be categorized into different types according to their physical characteristics, swelling characteristics, preparation method, ionic charge, and rate of degradation [21, 22].

They are increasingly being used as a versatile platform in the field of pharmaceuticals due to their excellent biocompatibility, high water absorption, and retention properties [23]. These unique characteristics of hydrogels make them suitable for various pharmaceutical applications such as drug delivery, wound healing, and tissue engineering. In drug delivery, hydrogels are used as carriers that

can interact with mucosal linings in different parts of the body such as the gastrointestinal tract, colon, vagina, and nose, allowing for a prolonged residence time at the local delivery. Additionally, the specific properties of hydrogels can be tailored using modification to achieve a wide range of functionalities. For instance, the controlled release of drugs can be achieved by incorporating stimuli-responsive functional groups, which respond to external stimuli such as pH, temperature, and light [24, 25].

Hydrogels in pharmaceuticals are a promising avenue for developing novel drug delivery systems and biomedical applications. Initial research on hydrogels began in 1894 when the application of inorganic salts led to the preparation of the first colloidal gel [26]. Also, Hydrogels can be classified as first-generation, second-generation, and third-generation hydrogels. PVA, PAM (polyacrylamide), PEG (polyethylene glycol) , and pHEMA (poly-2-hydroxyethyl methacrylate) hydrogels are known as first-generation hydrogels [27]. The current definition of hydrogel was established based on the groundbreaking work of Lim and Wichterle in 1960. They demonstrated the use of poly (2-hydroxymethyl methacrylate) gel-based materials to create soft contact lenses [3]. Mechanical fragility and inadequate oxygen transport were significant drawbacks of pHEMA hydrogels. In 1972, the freeze-thaw technique was used to prepare pHEMA hydrogels with pore sizes of several micrometers for the delivery of anti-inflammatory drugs and as space fillers in reconstructive surgery [27]. The first-generation hydrogels were initially designed with high swelling ratios and mechanical properties, but they did not exhibit responsiveness to environmental changes, such as temperature and pH [28]. In the early 1970s, researchers focused on preparing hydrogels that are responsive to changes in environmental conditions, including temperature and pH. Accordingly, the temperature-sensitive polyethylene glycol-polyester block copolymers, poly *N*-isopropyl acrylamide (pNIPAAm), and poly N-2-hydroxypropyl acrylamide (PHPMAm) hydrogels were referred to as second-generation hydrogels [11]. Temperature-sensitive hydrogels were used in situ because they can be easily injected into desired tissues and body cavities [29]. In the 1980s, pNIPAAm hydrogels were used to deliver progesterone, vitamin B12, and myoglobin. Third-generation hydrogels include stereocomplexed, cyclodextrins, and polyseudorotaxane hydrogels, most of which are cross-linked by physical interactions [27]. Stereocomplexed hydrogels are formed by coupling two complementary stereoregular polymers through stereoselective interactions. For example, injectable hydrogels were prepared through the stereocomplexation of PLLA (Poly-L-lactic acid) and PDLA (Poly-D-lactic acid) blocks to form an amphiphilic copolymer with increased thermal stability, mechanical strength, resistance to solvents, and protection against external forces penetration [30]. After 2010, the era of smart hydrogels began as a result of increased understanding of the structural and functional aspects of hydrogels. Smart hydrogels exhibit superior drug release kinetics and mechanical stability when used in drug delivery and implant preparation. Conventional hydrogels only undergo swelling and deswelling processes, while smart hydrogels can adapt to the environment and external stimuli, along with excellent self-healing ability. They can easily demonstrate gel-sol phase transition in response to small changes in environmental conditions [31].

It seems that hydrogels have great potential for repairing various skin injuries and wounds. The skin is the body's largest organ and serves as a crucial barrier, protecting the body from the external environment [32]. Although the human skin has a high capacity for self-regeneration, skin defects larger than a certain diameter will not heal spontaneously and require therapeutic intervention. Additionally, the wound-healing process is impaired in some patients, leading to chronic wounds that can eventually result in amputations or even death. Various dressings are utilized for wound healing and to protect wounds from various infections [33, 34].

However, traditionally gauze dressings were extensively used as healing agents. However, they suffer from many disadvantages such as delaying the healing process and causing pain when removed from the injured site [35, 36]. Ideal wound dressings should have excellent moisture retention properties, be free of toxic components, and maintain the optimum temperature at the wound site to reduce pain. Wound dressings should be cost-effective, minimize tissue trauma, and absorb wound exudate [37].

Hydrogels are considered the primary biomaterials for manufacturing wound dressings to treat burn wounds, owing to their hydrophilic properties and similarity to soft tissues. In addition, their proper biodegradability prevents secondary damage during dressing changes, making them ideal for use as biocompatible materials. Furthermore, in comparison to other emerging dressings like foams and films, hydrogels have a three-dimensional porous network similar to natural ECM. This network provides a framework for cell proliferation and migration [38-40].

Hydrogels create an optimal moist environment for the wound healing process, making them desirable for patients because of their cooling effect and non-adhesive properties. [41, 42]. While a moist wound environment is necessary for healing, it also raises the risk of microbial infections, which can exacerbate the wound and prevent the wound-healing process [43, 44]. The natural reparative and regenerative phases of the wounds fail to occur when they are colonized by opportunistic microbes[45]. In addition, uncontrolled infections disrupt the regeneration of anatomical and physiological structures, leading to the formation of chronic and non-healing wounds [46].To prevent and combat infectious conditions, advanced medical technologies rely on antimicrobial agents such as antibiotics, which work by either destroying pathogens or inhibiting their growth [47]. Therefore, hydrogels with antibacterial properties have great potential in clinical applications [48].

The pores and their sizes in the hydrogel structure play a crucial role in determining their drug-loading capacity and release profile in physiological fluids. The porosity of hydrogels can be controlled by adjusting their water affinity and cross-linking. Although the ability of hydrogels to absorb water can be adjusted by the number of hydrophilic groups along the polymer chains, the cross-linking density is determined by the concentration of cross-linking agents and the duration of cross-linking. The release of the loaded drug may be triggered by various controlling mechanisms, such as swelling, diffusion, environmental factors, and chemical stimulators [49]. Hydrogels are commonly used as hydrophilic materials for loading naturally occurring small molecules for therapeutic purposes. It is used to synergistically achieve precise

drug delivery and multiple biological functions to promote rapid wound healing. To enhance and maximize the bioavailability of curcumin, Pan *et al.* developed a bioactive using dynamic boronic ester to achieve the controlled release of curcumin.

Nutsarun *et al.* encapsulated quercetin in hydroxypropyl-β-cyclodextrin and PVA hydrogel to improve the therapeutic effectiveness of the biomolecule [50, 51].

Tao *et al.* (2021) prepared injectable semi-interpenetrating network hydrogels by blending a 2% (w/v) solution of sodium alginate with 0.5% (w/v) sericin protein and 0.6% (w/v) calcium gluconate. AgNPs, known for their antibacterial activity were also incorporated into a semi-interpenetrating hydrogel. The product caused a 99 % contraction of wounds on the 12th day, demonstrating excellent antibacterial activity. It also has a positive effect on the growth of fibroblasts and keratinocytes, which can promote wound healing [52].

Zahoor *et al.* (2023) have also developed a natural hydrogel by mixing silk sericin with carboxymethyl cellulose and PVA through repeated freeze-and-thaw cycles. Onion and banyan extracts were also combined in hydrogels. The treatment of diabetic mice with this hydrogel resulted in more effective diabetic wound contraction within 11 days [53].

Despite the successes of hydrogel-based delivery systems, challenges related to hydrogel drug delivery remain. These challenges include: the presence of a burst release at the time of administration, the limited ability to encapsulate certain categories of drugs (such as hydrophobic drugs, proteins, antibodies, and nucleic acids), the possibility of the growth of harmful microbes due to the high humidity of hydrogels, and the limited ability to fine-tune geometric patterns and shapes for precisely controlled drug release [54]. Despite these limitations, the use of hydrogels in treatment protocols will present challenges. The favorable and impressive characteristics of hydrogels have made them an attractive research field for overcoming the obstacles to their use.

NPs have the potential to overcome the limitations of hydrogels. The incorporation of NPs into the hydrogel structure(hydrogel composites) results in the controlled release of hydrophilic drugs, improved mechanical properties, the capacity to encapsulate hydrophobic or denatured molecules like proteins and peptides, and inhibition of bacterial growth in a moist environment.

2. The Role of NPs in Enhancing the Drug Delivery Properties of Hydrogels

In general, medications and numerous herbal compounds play a crucial role in wound healing. The loading strategy of drugs and plant compounds in hydrogels is determined by their nature. One of the effective and important strategies involves embedding NPs in hydrogels. Embedding NPs within hydrogels increases drug loading and enables controlled release.

Currently, the most widely used method to prevent wound infection is the local and systemic administration of antibiotics. However, the systemic administration of antibiotics is associated with

extensive side effects. On the other hand, the hydrophobic nature of antibiotics makes it difficult to load them into local hydrogels. Numerous studies suggest that employing polymeric and lipid NPs is a favorable option for incorporating antibiotics into hydrogels (Figure **1**).

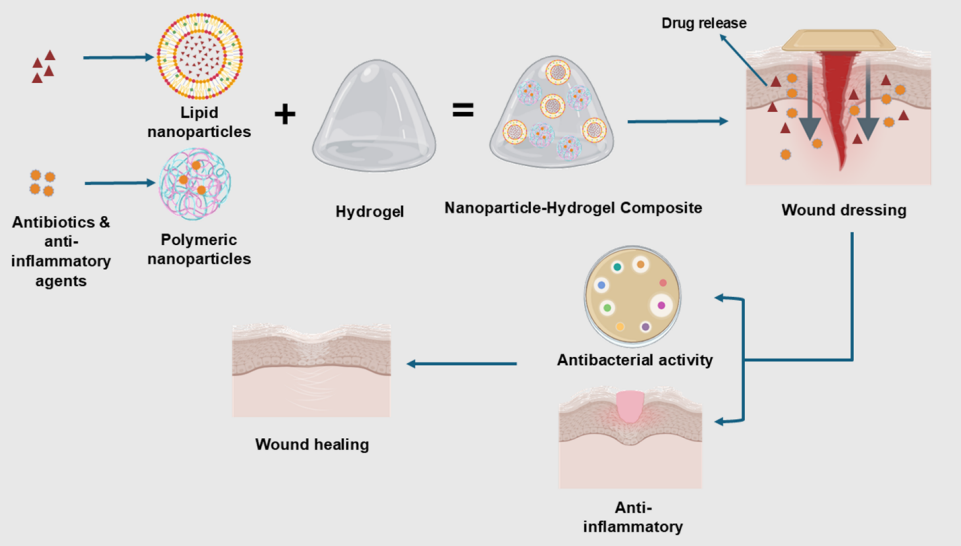

Figure 1: The Role of NPs in Enhancing the Drug Delivery Properties of Hydrogels.

Bengi Özkahraman *et al.* (2020) developed an effective delivery system for ampicillin by creating hydrogels embedded with NPs. Ampicillin was encapsulated within hyaluronic acid polymer NPs (250 nm in size), which were subsequently incorporated into a CS-gelatin hydrogel. Using this system, the drug loading was measured at 17.6%. 43% of the drug was released in the first 8 h, and the remaining amount was released within 5 days. The release kinetics of ampicillin from this system follow the Higuchi model, indicating a constant release of ampicillin. In this study, the antibacterial effectiveness of CS-gelatin hydrogel and CS-gelatin-HANp hydrogel was examined against *Staphylococcus aureus* (*S. aureus*) (gram-positive) and *Escherichia coli* (*E. coli*) (gram-negative) bacteria. The CS-gelatin hydrogel inhibited the growth of *S. aureus* bacteria because of the antibacterial properties of CS. On the other hand, in addition to inhibiting the growth of *S. aureus* bacteria, the CS-gelatin-HANp hydrogel also inhibited the growth of gram-negative *E. coli* bacteria [55]. C. Choipang *et al.* (2018) developed PVA hydrogels containing poly(lactic-co-glycolic acid) (PLGA) NPs loaded with ciprofloxacin (PLGA/CIP) for the treatment of infected wounds. After 4 days, the cumulative amounts of CIP released for the amounts of 6.25 mg, 39 mg, and 244 mg were 43.38%, 79.75%, and 94.63%, respectively. The highest cumulative amount of CIP released was observed when a higher concentration of CIP (244 mg) was loaded into the NPs. The challenge of the burst release of CIP from the hydrogel, which is not unexpected due to the hydrophilic nature of CIP, was addressed by utilizing PLGA NPs. The controlled release of this antibiotic was facilitated by PLGA NPs embedded in PVA hydrogel. In this study, the antibacterial activity of each of 6.25 mg, 39 mg, and 244 mg was measured. It was found that these concentrations strongly inhibited E. coli with minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values. The bactericidal

effects for three concentrations of 0.5 µg/ml, 0.625 µg/ml, and 0.325 µg/ml are inhibited, respectively. Also, MIC and MBC values for *S. aureus* bacteria were recorded for three concentrations, 1.5 μg/ml, 0.5 μg/ml, and 0.3 μg/ml, respectively [56]. In 2020, Sukanjana Kamlungmak *et al.* utilized a temperature-sensitive poly hexamer-PVA hydrogel to encapsulate gelatin v containing mupirocin (MLH). Due to the relatively lipophilic nature of mupirocin, the incorporation of gelatin NPs ensures optimal dispersion of this antibiotic and facilitates its controlled release through diffusion that adheres to first-order kinetics. The antibacterial efficacy of the mupirocin-loaded gelatin nanoparticle hydrogels was assessed against the bacterial species *S. aureus*, *Staphylococcus epidermidis* (*S. epidermidis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *E. coli*. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data indicated that the mupirocin-gelatin nanoparticle hydrogel exhibited lower MIC and MBC values compared to mupirocin ointment. The team continued their research in 2022 by investigating the effects of mupirocin-loaded hydrogels (MLH) on methicillin-resistant *S. aureus* (MRSA) bacteria. They compared hydrogels containing mupirocin NPs with pure mupirocin. Inhibition of bacterial growth was observed rapidly, within just 1 h of treatment. After 12 h, both mupirocin and MLH effectively inhibited isoleucyl-tRNA synthetase in MRSA [57, 58].

In addition to the importance of prescribing antibiotics for the healing and repair process, it is essential to utilize other anti-inflammatory and wound healing agents. An ideal dressing should not only reduce inflammation but also stimulate the healing mechanism and accelerate wound closure [59]. On the other hand, the continuous release of free radicals at the wound site activates the inflammatory response, which impairs wound healing. Therefore, effectively reducing the levels of free radicals in the wound can facilitate the healing process. Curcumin is one of the most potent antioxidant compounds that can significantly accelerate wound healing [60]. Although the incorporation of curcumin into wound healing hydrogels is a promising strategy, its poor water solubility, rapid degradation, and metabolism unfortunately limit its medical applications. To maximize the benefits of this therapeutic molecule, researchers have pursued the design of curcumin nanoformulations, which provide a more effective means of utilizing curcumin for wound healing purposes [61]. Sarah A. Sideek and colleagues, by loading curcumin-containing bilosomes into an alginate dialdehyde hydrogel. This approach not only facilitated the controlled release of curcumin but also demonstrated the enhanced efficacy of the curcumin-loaded bilosome hydrogel in wound healing. Remarkably, the size of the wounds was completely reduced after three weeks due to the programmed healing mechanism, resulting in fully closed wounds [62]. Also, the effects of curcumin nanoemulsion loaded in Carbopol 934 hydrogel on wound healing were investigated by Thi Thanh Ngoc Le *et al.* This study found that, with a controlled release of curcumin over 14 days, the curcumin-loaded nanoemulsion-based gel was significantly more effective than both the commercial formula and the formulation containing pure curcumin, as evidenced by macroscopic findings [63].

Other flavonoids, such as quercetin, exhibit potent antioxidant properties. Quercetin also enhances fibrosis-related signaling pathways by promoting fibroblast proliferation and altering signaling

mechanisms. However, due to its hydrophobic nature and low bioavailability, a liposomal carrier is utilized for its administration. Therefore, in the present study, quercetin-loaded liposomes (QLH) were designed to enhance bioavailability and regulate quercetin transport at the wound site. In a study conducted by Rajendra Jangde *et al.*, a two-step delivery system consisting of quercetin liposomes incorporated into a porous carbopol hydrogel was developed to improve quercetin bioavailability. The in vivo performance of this nanohybrid hydrogel for wound healing was evaluated histologically. The results indicated accelerated wound healing, with a significant reduction in wound closure time compared to conventional dosage forms. The in vitro and in vivo findings of this study suggest a reliable therapeutic approach for wound healing [64].

The role of plant essential oils in reducing infections and accelerating the wound-healing process is significant. Kun Cai *et al.* demonstrated the antibacterial and wound-healing effects of eucalyptus essential oil, employing a nanoemulsion-based strategy to address the instability of the essential oil and enhance its long-term antibacterial performance. Eucalyptus nanoemulsions were incorporated into a hydrogel matrix composed of carbomer 940 (CBM) and carboxymethyl chitosan (CMC). In vivo experiments revealed that the CBM/CMC/EEO nanoemulsion effectively reduced the bacterial load in wounds and accelerated the recovery of epidermal cells and skin tissue. Furthermore, the anti-inflammatory properties of the CBM/CMC/EEO nanoemulsion were evidenced by a reduction in the expression of two inflammatory factors, IL-6 and TNF-α, alongside an increase in the expression of three growth factors: TGF-β1, VEGF, and EGF [65].

The wound-healing properties of *Achyrocline satureioides* (*A. satureioides*) extract are well-documented. However, due to its low aqueous solubility, Lucélia Albarello Balestrin's research group has explored the feasibility of preparing nanoemulsions containing *A. satureioides* extract and has assessed their potential for topical application in wound healing. Their studies demonstrated in vitro cell proliferation, keratinocyte migration, and a lack of cytotoxicity [13]. Subsequently, they designed and fabricated hydrogels by incorporating the gelling agent Carbopol into the nanoemulsions containing *A. satureioides* extract, resulting in a topical formulation for wound healing. This formulation enhanced angiogenesis by up to 20%, reduced inflammation (as indicated by decreased tumor necrosis factor α) by up to 35%, and improved re-epithelialization in lesions, thereby promoting overall wound healing. Furthermore, the application of this topical formulation resulted in an increased number of blood vessels and hair follicles in the treated wounds compared to the control group [66].

3. The Role of NPs in Enhancing the Anti-bacterial Properties of Hydrogels

Enhancing the antibacterial properties of wound-healing hydrogels is an effective strategy for improving the wound-healing process (Figure **2**). For instance, the antibacterial effects of AgNPs have been recognized for many years [67]. One of the most desirable characteristics of Ag is that its toxicity

and lethality to human cells are significantly lower than those to bacteria, making it an ideal choice for enhancing the antibacterial properties of hydrogel wound dressings [68].

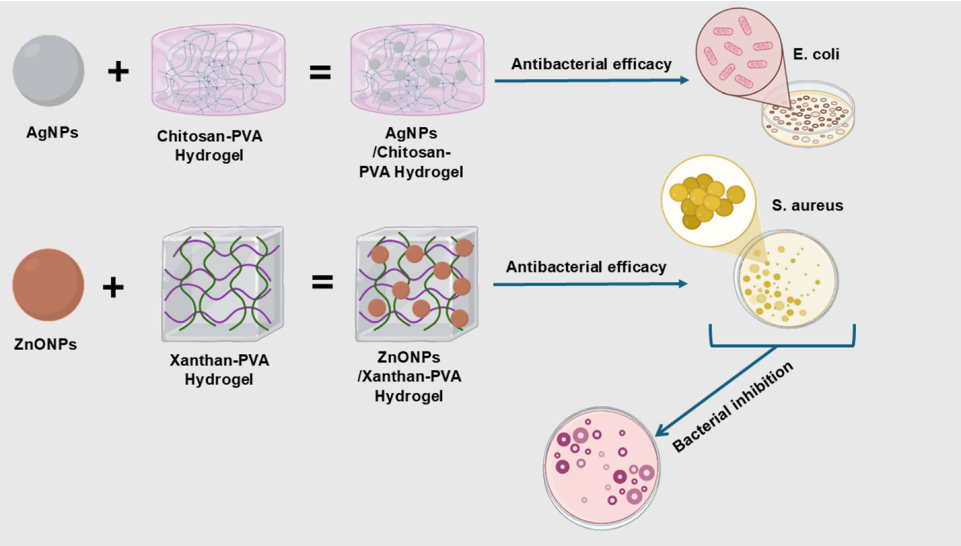

Figure 2: The Role of NPs in Enhancing the Anti-bacterial Properties of Hydrogels.

In a study, Katarina Nešović *et al*. presented non-cytotoxic CS and PVA hydrogel wound dressings embedded with AgNPs that possess physicochemical properties exhibiting potent antibacterial activity against *S. aureus* and *E. coli*. For both bacterial strains, the AgNPs hydrogels (0.25 Ag/PVA/0.1CHI and 0.25 AgPVA/0.5CHI) resulted in a complete reduction of bacterial cell numbers after just 1 h of incubation. Notably, in the case of *S. aureus*, there was a significant reduction of 4 log units within 15 min. This rapid decline in bacterial growth prevented biofilm formation. In contrast, hydrogels without AgNPs achieved a 100% reduction in *S. aureus* cell numbers after 1 h. However, for *E. coli*, the PVA/0.1CHI and PVA/0.5CHI hydrogels did not demonstrate a significant inhibitory effect; only after 24 h of incubation did the PVA/0.5CHI show notable efficacy. This bactericidal effect can be attributed to the inherent antibacterial properties of CS. However, as the CS surface becomes saturated with dead bacterial cells, it gradually loses its antibacterial activity over extended periods [69]. Xushan Chen and colleagues developed an organic-inorganic hydrogel composed of oxidized dextran (ODex) and hyaluronic acid-linked adipic dihydrazide (HA-ADH). By incorporating quaternary CS and AgNPs into the hydrogel, they confirmed the synergistic antibacterial effects of CS and AgNPs. In this study, the ODex/HA-ADH hydrogel exhibited no antibacterial properties, whereas the antibacterial efficacy of the Ag@ODex/HA-ADH/HACC hydrogel was significantly greater than that of the ODex/HA-ADH/HACC hydrogel. This enhanced antibacterial activity can be attributed to the combined effects of AgNPs and HACC. The inhibition zones of the ODex/HA-ADH/HACC hydrogel against *E. coli*, *S. aureus*, and *P. aeruginosa* were measured at 16 mm, 20 mm, and 17 mm, respectively. In contrast, the inhibition zones of the Ag@ODex/HA-ADH/HACC hydrogel were 24 mm, 24 mm, and 27 mm for the same bacteria [70].

However, a significant challenge associated with AgNPs is their instability in aqueous media. To address this limitation, Jyoti Verma *et al.* coated AgNPs with sericin and CS, subsequently incorporating the coated NPs into a carbopol hydrogel to create an effective wound dressing. In the case of *E. coli*, S/C SNPs G-1 exhibited higher zone of inhibition values (21.0 ± 1.5 mm) compared to SNPs (8.0 ± 1.5 mm) and S/C SNPs (1.38 ± 13.0 mm), respectively. Similarly, in the case of *S. aureus*, S/C SNPs G-1 demonstrated greater effectiveness, achieving a maximum zone of inhibition of 1.45 ± 0.17 mm, compared to SNPs, which had a zone of inhibition of 1.0 ± 0.7 mm [71].

Although AgNPs are highly efficient antibacterial agents, their high production costs limit their use in medical applications [72]. Recently, ZnO NPs have emerged as a promising alternative with antibacterial properties [73].

In a study, Amany I. Raafat *et al.* developed nanocomposite hydrogels composed of xanthan, PVA, and ZnONP for use as antibacterial wound dressings. The results indicate that increasing the concentration of ZnONP from 0% to 5% by weight resulted in an inhibition zone that expanded to 2 cm for *E. coli* and 4 cm for *S. aureus* [74]. Mohammad Taghi Khorasani *et al*. enhanced the antibacterial properties of heparinized PVA/CS hydrogels by incorporating ZnONPs. The inhibition zone in the hydrogel without ZnONPs measured 20 cm, attributed to the CS polymer. In contrast, the hydrogel sample containing 1 wt% zinc NPs exhibited inhibition zones of 23 cm and 26 cm against *E. coli* and *S. aureus*, respectively. These results confirm the synergistic effect of ZnONPs and the CS polymer [75]. This synergy was also confirmed by Shaghayegh Baghaie *et al.* The hydrogels used as wound dressings are composed of PVA polymers, CS, starch, and embedded ZnONP. By increasing the CS content to 10% by weight in the hydrogel, it was observed that the inhibition zones for *E. coli*, *S. aureus*, and *P. aeruginosa* were 15 mm, 16 mm, and 16 mm, respectively. However, when 0.1% by weight of ZnONP was added, the inhibition zones for *E. coli*, *S. aureus*, and *P. aeruginosa* increased to 23, 24, and 16 mm, respectively [76].

4. The Role of NPs in Enhancing the Mechanical Properties of Hydrogels

One of the significant challenges in the application of hydrogels is their low mechanical strength. PVA is a hydrophilic polymer that serves as a suitable option for creating wound-healing hydrogels due to its excellent water absorption capacity, biocompatibility, and non-toxicity. However, its low mechanical strength, poor elasticity, and lack of adhesion in the swollen state present limitations to its application. One effective strategy to address these limitations is the incorporation of nanocellulose crystals. Weijun Yang *et al*. demonstrated that the compressive strength of PVA hydrogel increased from 0.51 MPa to 0.70 MPa with the addition of 2 wt% cellulose nanocrystals (CNC). Furthermore, when 2 wt% lignin NPs (LNPs) were included, the compressive strength rose to 0.63 MPa. The adhesion strength of the PVA hydrogel loaded with CNC and LNP was measured at 0.15 ± 2.78 KPa, which is a promising value for the potential use of this hydrogel as a wound dressing material. Rheological studies also indicated that the addition of

CNC and LNP significantly enhanced the mechanical properties of the hydrogel [77]. Mojtaba Koosha and colleagues also reinforced nanofibrous hydrogels composed of PVA and CS with halloysite nanotubes (HNT). They observed that the addition of 3% and 5% HNT to the PVA/CS nanofibers increased adhesion by 2.4 and 3.5 times, respectively. Furthermore, the incorporation of HNT into the CS/PVA nanofibers enhanced the hydrophilicity of the HNT-reinforced nanofibers, facilitating the attachment of fibroblast cells [78].

In a study conducted by Ying Chen *et al.*, LNPs were utilized to enhance the properties of polyacrylamide hydrogel. The incorporation of 23.5% LNPs resulted in an increase in fracture stress from 0.04 MPa to 7.87 MPa, along with a 45.8% increase in critical strain. The tensile strength and elongation at the break of the polyacrylamide hydrogel were measured at 38 kPa and 190%, respectively; these values improved to 110 kPa and 750%, respectively, with the addition of LNPs [79].

In addition to NPs, nanofibers can serve as an excellent reinforcement for wound dressing hydrogels. Azadeh Ghaee *et al.* utilized PEGMA-modified polycaprolactone (PCL) nanofibers to enhance CS/gelatin hydrogels. By increasing the concentration of modified PCL nanofibers within the CS/gelatin hydrogel scaffold, both the compressive strength and the compressive modulus of the scaffolds were significantly improved [80].

CS wound dressings have recently garnered significant attention from researchers in the field of wound care. Although CS is a non-toxic, biodegradable, and biocompatible polymer, it possesses certain inherent disadvantages, such as relatively poor mechanical properties. F. Dong *et al.* utilized cellulose nanocrystals to enhance these mechanical properties. The tensile strength of wet CS hydrogel was measured at 0.9 MPa; however, the incorporation of 10% cellulose nanocrystals increased this value to 3.9 MPa. Additionally, the tensile modulus of the CS hydrogel rose from 0.7 MPa to 6.3 MPa with the addition of 10% cellulose nanocrystals, while the elongation at break decreased from 65% to 30% [81]. Additionally, Yajuan Xie and colleagues observed that by incorporating 3 mg of AgNPs into CS hydrogel, the compressive fracture stress increased by 15 times, and the strain increased by 25 times [82].

5. Conclusion and Perspective

Hydrogels, which are three-dimensional polymeric structures capable of absorbing and retaining significant amounts of water, play a crucial role in wound healing and drug delivery. These materials have been extensively utilized in tissue engineering, wound care, and drug delivery systems due to their high biocompatibility and potential for chemical modification. However, certain limitations, such as inadequate mechanical strength, suboptimal drug release control, and the risk of microbial contamination, present challenges for their clinical applications. To address these issues, the incorporation of NPs into hydrogels has been proposed as an innovative approach to enhance the properties of these materials. Research indicates that NPs not only improve mechanical strength and enable more precise control over drug release but also augment antimicrobial properties and enhance therapeutic efficacy.

With the advancement of nanotechnology and biomaterials, it is anticipated that more sophisticated hydrogels capable of responding to biological and environmental stimuli will be developed in the future. Specifically, the design of hydrogels that can autonomously react to changes in pH, temperature, or biological signals from the body will open new avenues for disease treatment and tissue regeneration. Furthermore, innovations in 3D bioprinting and bioengineering technologies will facilitate the creation of personalized hydrogels that can be precisely tailored to meet individual patient needs. Overall, the integration of hydrogels with nanomaterials and emerging technologies will pave the way for the development of advanced bioscaffolds, next-generation wound dressings, and intelligent drug delivery systems.

Ethical Issue

Authors are aware of and comply with, best practices in publication ethics specifically about authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests, and compliance with policies on research ethics. The authors adhere to publication requirements that the submitted work is original and has not been published elsewhere in any language.

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