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RESEARCH ARTICLE

A REVIEW ON POLYMER-ZINC OXIDE HYDROGELS FOR WOUND HEALING

M. Krishna Veni [1], J. Indira[1,*] and K. Santhiya[1]

[1,*]Vellalar College for Women (Autonomous), Thindal, Erode – 638012, Tamil Nadu, India.
Email: indira@vcw.ac.in

Abstract

Background & Aims

Recovery of wound is an intricate process. The stages of wound healing consist of four stages. Hemostasis, Inflammation, Proliferation, and Remodeling phases are overlapping with each other. Growth factor is an essential key role in wound healing and it is a specific endogenous polypeptide secreted by six cells such as platelets, macrophages, keratinocytes, fibroblasts, mast cells and neutrophils. Over the past few decades, researchers have used hydrogels to generate wound dressing material.

Methods

In this study, a systematic review of all published articles in Elsevier, MDPI and cell Press from 2016 to 2024 was conducted to investigate the several polymer zinc oxide hydrogels involved in wound healing.

Results

Hydrogels are three-dimensional polymeric materials and porous in nature. Hydrogels are extensive properties such as excellent biocompatibility, biodegradability, water imbibing capacity and non-toxicity. However, hydrogels have relatively little antibacterial activity. To combat this problem, zinc oxide hydrogel with bioactive ingredients such as polymers are a promising option for wound treatment. Zinc oxide nanoparticles are even in trace amount is considered as crucial for wound healing application. Hydrogels' crosslinking and hydrophilic properties allow them to absorb enormous amounts of water to promote wound healing.

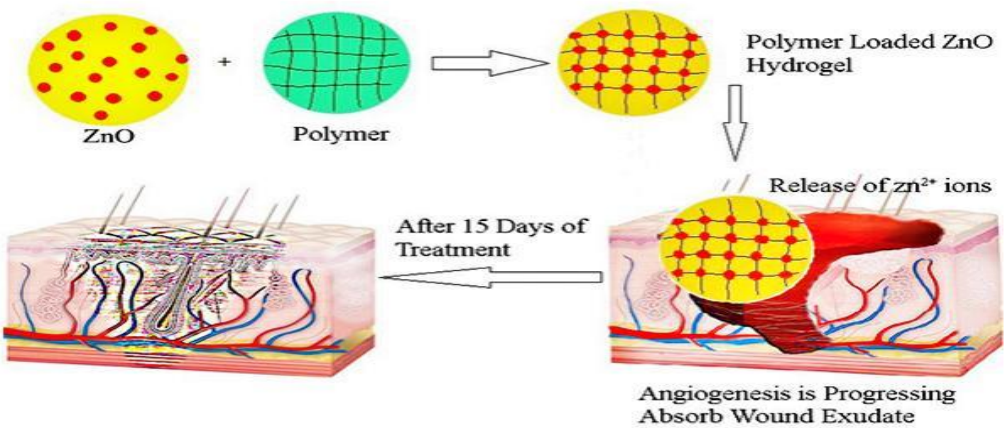
Conclusion

This review summarised up by outlining the present obstacles and potential paths forward for polymer-ZnO hydrogel optimization as next-generation wound care materials.

KEYWORDS

Polymer, Zinc Oxide, Hydrogel, Wound healing, Nanofiber, Extracellular matrix.

Graphical Abstract :



The Schematic illustration show the formation of zinc oxide hydrogel effectively inhibits bacterial growth and promotes a clean wound environment for rapid healing

Introduction

Hydrogels are promising material composed of both natural and synthetic polymers. Hydrogel synthesis involves the utilization of natural polymers such as chitosan, collagen, alginate, hyaluronic acid, starch, acacia gum, dextran, gelatin, fibrin, and silk fibroin. Hydrogels made of zinc oxide have antibacterial and hinder the oxidative stress. In addition to ensuring the wound healing process, zinc oxide hydrogels give moisture to the wound site. 3D printed hydrogel framework are used in dressing material as novel for wound treatment. Electrospinning is a highly efficient and economical technique for creating polymeric nanofibers with various structures, including hollow, porous, and core-shell nanofibers. Antibiotic resistance in humans is caused by the excessive use of oral antibiotics. Polymer hydrogel dressing is used to prevent this issue. Hydrogels are used in more diverse areas like tissue engineering, gene therapy, wound care, skin grafts, drug delivery, 3D bio-printing, dye removal from the textile industry and harmful micro-pollutants from industrial wastewater.ZnO polymer hydrogel is a promising material to catalyze the angiogenesis process. Zinc oxide possesses multifunctional property such as low cytotoxicity, anti-microbial activity, anti-inflammatory and anti-oxidant property will promote rapid healing when incorporated with Hydrogels [1]. Now Let us discuss the various polymer-ZnO hydrogel for wound healing application.

1. Chitosan Incorporated Zinc Oxide Hydrogel

Chitosan is a natural polymer that can be extracted from chitin. It can be found in crustaceans and insects. Reza Monfared et al., [2] developed a double-layered sponge that contains zinc oxide is incorporated with chitosan, carbon dots and sodium alginate used as a wound dressing. It mimics the composition and functions of Extra Cellular Matrix. Zinc Chloride is a precursor for Zinc Oxide nanoparticle and glutaraldehyde acted as a cross linking agent. Three different concentrations of Zn, 1 %, 2 % and 4 % were studied and compared the results with pristine and the concentration of Zn was optimized as 4 % which exhibited good result. The prepared zinc oxide hydrogel was employed *in vitro* blood clotting and anti-bacterial activity. The research group further investigated the morphology of the hydrogel. The TEM image reveals the morphology of spherical particles are less than 100 nm in size. The SEM image demonstrates that the hydrogel has a double layer and uniformly connected porous network. The porosity of hydrogel is essential for the angiogenesis process. The research team found that porosity of the hydrogel decreases as the concentration of Zn nanoparticles increases. More exudate can be absorbed from the infected wound site because of high porosity of great wound dressing material. The contact angle of oxide hydrogels were less than 90, shows it is hydrophilic in nature. The research team further investigated about the water retention efficiency of the as-synthesized Hydrogel's and they found that zinc oxide hydrogel exhibit higher value of 34.3 % than the hydrogel without ZnO. The research group also investigated the antibacterial activity of the hydrogel against gram-positive bacteria Staphylococcus aureus and gram-negative bacteria Pseudomonas aeruginosa by agar disk diffusion method. These are the two important bacteria cause wound infection. The inhibition zone of P.aeruginosa was 41mm for 4 % ZnO hydrogel sample, which is greater than ciprofloxacin inhibition zone 36 mm. The inhibition zone of S.aureus was 25 mm of 4 % ZnO hydrogel. This sponge hydrogel is more resistant to gram-negative bacteria. The research team further revealed that Chitosan-ZnO hydrogel facilitate the rapid blood clot [6].

Elmehbad et al., [3] synthesized 1 % and 3 % ZnO hydrogels at two distinct chitosan chains. Oxalyl dihydrazide was used to crosslink between the chitosan Schiffs base (OCsSB) and chitosan chain (OCs). Antimicrobial inhibition evaluated by Minimum inhibitory concentration assay, Minimum biofilm inhibitory concentration assay and Anti-clostridium difficile activity assay. Human lung fibroblast cells were used to study cytotoxicity, which was found to be safe for human cells. XTT assay measured by four Gram positive and four Gram negative bacteria and compared by vancomycin. When it comes to inhibitory activity of chitosan chain performs better than oxalyl dihydrazide. It will employed in the pharmaceutical industry.

2. Chitosan and Polyvinyl Alcohol Incorporated Zinc Oxide Hydrogel

Khorasani et al., [4] reported the formation of hydrogels using PVA and chitosan combined with zinc oxide nanoparticles. Freeze-thaw method was used to synthesize hydrogel by varying thawing time, thawing temperature and F-T cycles. The addition of PVA creates an interpenetrated network of polymers, which gives the material its elastic and rubbery qualities while also being non-toxic and non-carcinogenic. The research team investigated anti-bacterial property, biocompatibility, *in vitro* wound healing, cytotoxicity, morphology and mechanical properties and they found that at -20 °C, the polymer chain freezes. The FTIR and XRD results supports the formation of ZnO in chitosan-PVA-ZnO hydrogel. The Scherrer equation yielded average dimensions of 18 nm for the nano ZnO structure, which was hexagonal wurtzite. They identified the average pore size of 13.5 micrometer from SEM investigation and at 5 °C and 6 F-T cycles, the time dropped to 2 hours, and the pore size increased to 19.1 micrometer. Whereas the temperature increased to 15 °C and 6 F-T cycles, the time 4.65 h average pore size again increased to 18.2 micrometer. The research team also investigated the biocompatibility of hydrogels in L-929 and HDF cells and the results indicated that no toxicity. Furthermore, they evaluated the antibacterial activity by disc diffusion method against E.coli and S.aureus and the results demonstrated higher inhibition zone was observed in S.aureus.

3. Gelatin Incorporated Zinc Oxide Hydrogel

Ya-Chu Ya and coworkers [5] developed gelatin composite hydrogel with zinc oxide nanoparticles by in situ form. Initially, they form a polypeptide chain of gelatin, when it reacts with methacrylic anhydride. Further they added a photo initiator 2-hydroxy 4-(2-hydroxyethoxy)-2-methyl propiophenone to the gelatin composite hydrogel to form polypeptide chain. The research team prepared Zinc oxide nanoparticles at three different concentrations 1, 10, 30 mM. From SEM results they revealed that the particle size of hydrogel was in the range of 12–14 nm. According to TGA data, they confirmed that zinc oxide hydrogel had greater thermal stability. When an increases the zinc oxide concentration the swelling ratio falls to aid the healing process. The antibacterial study was evaluated by CFU assay and the inhibition percentage in EHEC 99.89 %, S.flexneri 99.78 % and 98.98 % in S.aureus. The cell viability assay test was performed using NIH 3T3 and BEAS-2B cells and the results showed above 70 % demonstrated the recommendation of hydrogel in biomedical engineering.

Another hydrogel consisting of Zinc doped cerium oxide nanoparticles combining methyl acrylate gelatin which is modified with dopamine was reported by Zhoa et al. [6]. Antibacterial activity, *in vitro* biocompatibility, *in vivo* wound healing, *in vitro* antioxidant and proangiogenic properties were evaluated and they found that the inhibition efficiency in E. coli and S. aureus were 70% and 80 % respectively. This doped hydrogel showed higher wound closure rate of 98.5 % in rat model at 14 days of treatment.

Liu et al., [7] developed gelatin, tannic acid and oxidized sodium alginate with zinc oxide nanoparticles. *In-vitro* swelling property, Zn^{2+} release assay, *in vitro* antioxidant activity, *in-vitro* antibacterial activity, hemolysis assay and cytocompatibility assay were examined to study how the hydrogel stimulates the wound healing process. The research team found that Zn^{2+} ions are released continuously, killing bacteria at the wound site. The release rate was 0.54 mg/mL in 48 h. The *in vitro* coagulation property is connected to the crosslinking structure of the hydrogel. The blood clotting function of gelatin composite hydrogel is greater than the blood's own clotting time which may due to the positively charged amino group on the hydrogel electrostatically interacting with the negatively charged platelets. The property of antibacterial activity measures the hypostatic rate of S. aureus and E. coli and it was 97.8 % and 96.6 % respectively. The developed multifunctional hydrogel was acted as a wound dressing material with therapeutic impact.

4. Cellulose and Grape Fruit Seed Extract Incorporated with Zinc Oxide Hydrogel

Dharmalingam and co-workers [8] fabricated ether derivatives of cellulose fabricated with zinc oxide in presence of three distinct concentrations of grapefruit seed extract (GFSE) 0.25 %, 0.5 % and 1 %. Citric acid was added as a crosslinking agent. sodium carboxy methyl cellulose and hydroxyl propyl methyl cellulose were ether derivatives of cellulose that are hydrophilic, biocompatible and biodegradable. The ester, OH and carbonyl groups in the zinc oxide hydrogel were confirmed by FTIR data. The polymer and citric acid react to generate an ester bond. The Raman spectrum showed the primary characteristic peak of wurtzite ZnO. They prepared hydrogel films of 30-100 nm in size which was confirmed by FESEM analysis. GFSE concentration increases structural changes occur in hydrogel film leads to decreased tensile strength. Highest elongation value was observed in 1 % GFSE hydrogel film. The antioxidant activity was followed by DPPH assay revealed 1% of GFSE have more inhibition of DPPH free radical. The anti-bacterial activity was measured in E.coli and S.aureus bacteria. The research team found that as the concentration of GFSE increases the antibacterial activity increases. Hence this research team underlined that ZnO in the hydrogel favor the healing of wound.

5. Cysteine Conjugated Chitosan-Cellulose Hydrogel with Zinc Oxide Nanoparticles for Naringenin Drug Delivery

Dhanya George and coworkers [9] developed chitosan–cellulose conjugated with cysteine incorporated zinc oxide nanoparticles to employ Naringenin drug release. Cysteine is an essential precursor for glutathione synthesis. Dialdehyde cellulose as a green crosslinker derived from sugarcane bagasse. Naringenin is a flavone with excellent anti-oxidant and anti-inflammatory properties. The research team investigated about the biological performance of cysteine conjugated chitosan-cellulose hydrogel with ZnO nanoparticles and the biological studies include biocompatibility, anti-microbial and anti-cancer. Naringenin drug release was carried out in varying pH 5, 6.8 and 7.4. At acidic pH 5 shows better drug release of about 72.78 % in 12 hours and where the initial concentration of drug was 1.0 mg/ ml. The L-929 fibroblast epidermal cells were utilized for anti-bacterial activity in S.aureus. Anti-fungal activity executed in Trichophyton rubrum. They found that the antibacterial activity increases as the concentration of ZnO and drug increases. Cysteine conjugated with chitosan and cellulose plays a major role in apoptosis and exhibit more cell viability and act as a cytoprotective activity against programmed cell death. The anti-cancer activity carried out in human skin cancer cells such as A431 showed great performance against skin carcinoma. Hence the researcher ensured that the prepared hydrogel is suitable for both microbial infection and skin cancer treatment.

6. Gum Acacia and Poly Sodium Acrylate Hydrogel Loaded with Zinc Oxide Nanoparticles

Bajpai et al., [10] synthesized zinc oxide nanoparticles loaded with gum acacia and sodium acrylate in-situ form by hydrothermal method. Potassium persulphate as an initiator for this reaction. N, N – methylene bis –acrylamide as a cross linking agent. The formation of ZnO nanoparticles within the hydrogel matrix was assessed by surface Plasmon Resonance Spectrum showed a sharp peak at 364 nm. The research group confirmed the hydrogel matrix by XRD and FTIR results. They evaluated the swelling behavior of hydrogel in phosphate buffer saline at pH 7.4 by gravimetric method. According to SEM analysis they revealed the average size between 40- 60 nm. Anti-bacterial activity against E.coli bacteria was studied and the inhibition zone was 3.2 ± 0.07 mm. So this hydrogel is suitable for biomedical application.

7. Sodium Alginate Embedded with Zinc Oxide Nanoparticles for Chronic Wounds

The development of 3D-printed sodium alginate hydrogel impregnated with zinc oxide nanoparticles was reported by Cleetus et al. [11]. Calcium chloride was employed as a crosslinker. Rheological analysis, cytocompatibility, humidity sensor, swelling assay were analyzed. The characteristic XRD peaks are quite crystalline and resemble the JCPDS data card. SEM results revealed that synthesized zinc nanoparticles are spherical in shape and homogeneous size distribution, with a particle size of 4-6 nm. Staphylococcus epidermidis, which causes common wound infections, has been the subject of an antibacterial investigation. The growth of bacteria was inhibited by the addition of zinc oxide. Swelling behavior was examined in manually casted gels and 3D bio-printed gels. From this result, 3D bio-printed gels have a prominent wound healing scaffold. Hence, Zinc oxide-loaded 3D-printed hydrogels showed significant promise as an antimicrobial treatment for chronic wounds.

8. Poly Acrylic Acid and Polyvinyl Pyrrolidone Hydrogels Incorporated with Zinc Oxide Nanoparticles

By free radical polymerization approach, Mohsen Shahrousvand et al. [12] created a novel wound dressing material by combining zinc oxide hydrogel with PAA and PVP polymer hydrogel. In hydrogel synthesis potassium persulphate is used as an initiator while N, N- methylene bisacrylamide is a crosslinker. Due to their high solubility in water, PAA and PVP are referred to as superabsorbents because of their increased ability to absorb and hold onto water. PAA can break down the cell membranes of bacteria that cause infections, which increases antibacterial activity. Zinc concentrations include 0 %, 1 %, 2 % and 4 %, whereas PVP percentage ranges from 0 to 2.5, 5, 7.5 and 10. The team observed that the swelling behavior of the hydrogel because it allows the body to absorb more exudate from the wound. More water absorption behavior was exhibited by the 7.5 % PVP sample, making it appropriate for used as a dressing material. From SEM investigation, they revealed that PAA and PVP had a strong polar interaction. Further, they found that during TGA analysis, zinc oxide material remains in the structure where hydrogel degraded in the form of gas. Anti-bacterial activity was examined in S.aureus and P.aeruginosa bacteria. The Research team investigated their newly designed wound dressing material in a rat excisional wound model, the result revealed that complete wound closure was observed after 21 days of treatment. Hence the team insisted this PAA-PVP-ZnO hydrogel can act as a good choice of dressing for wound healing.

9. Berberine Encapsulated with Zinc Oxide Nanocolloids Hydrogel

Xuechen yin et al., [13] developed berberine encapsulated with zinc oxide nano colloids in injectable form. Polyvinyl alcohol, sodium alginate, berberine, zinc sulphate were the precursors for hydrogel preparation. The hydrogel have superior antifungal, antibacterial, anti-oxidative stress and anti-inflammatory qualities are the key results of the bioactive component berberine. In diabetic patients, the accumulation of reactive oxygen species causes a delay in the wound-healing process. The prepared ZnO-Berberine polymer hydrogel could eliminate reactive oxygen species when treated with fibroblast cells. The intensity of UV spectrum peak increased denotes the stable release of berberine from the hydrogel. After 15 days of treatment, the wound healing rate in rats by *in vivo* test was 92.9 %.

CONCLUSION

In this review, several polymers were incorporated with zinc oxide hydrogel which has significant potential for wound healing due to its ability to encourage wound closure, fight bacterial infection and enhance tissue regeneration. These polymer hydrogels have an active anti-S. aureus bacterial effect. Despite these benefits, issues including optimizing ZnO concentration, ensuring stability over time and reducing cytotoxicity must be resolved for broad clinical application. Enhancing the formulation, investigating new biomaterials for synergistic effects, and carrying out comprehensive clinical trials to confirm their safety and effectiveness should be the main goals of future research. Hydrogel wound dressing material is a great alternative to conventional dressings because of its self-healing properties. Overall, ZnO hydrogels represent a promising and creative approach to wound care treatment.

AUTHOR CONTRIBUTIONS

M. Krishna veni: Writing - original draft; Methodology; Project administration; Resources; Writing – review & editing. J. Indira: Investigation; Supervision; Validation; Formal analysis. K. Santhiya: data curation, software.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author, Krishna Veni, affirms that this manuscript is an honest, accurate, and transparent account of the study being conducted reported.

DATA AVAILABILITY STATEMENT

As this study is a systematic review, no original data are available in the original and supplementary data.

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