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Design and Characterization of Stimuli Responsive Nanohydrogel as Wound Dressing Material Impregnated with Zinc Oxide and Iron Oxide Nanoparticles

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Abstract:

Recent advances in wound care have been propelled by the integration of stimuli responsive materials and innovative technologies, enabling the development of responsive and adaptive solutions. This paper presents a **Stimuli responsive Nanohydrogel as wound dressing material** that leverages the unique properties of zinc oxide (ZnO) and iron oxide (Fe_2O_3) nanoparticles to enhance wound healing and provide real-time monitoring capabilities. Material is designed using a hydrogel matrix, which is embedded with tracking key wound parameters, such as pH, temperature, moisture levels, and glucose concentration. Zinc oxide(ZnO) and iron oxide (Fe_2O_3) nanoparticles provides the material with enhanced antimicrobial properties, promoting a sterile healing environment and reducing the risk of infections. Additionally, these nanoparticles support tissue regeneration and possess anti-inflammatory properties, contributing to accelerated wound healing. **Stimuli-responsive nanohydrogel** works as a control unit, allowing for dynamic adjustments in drug release and moisture retention to match the wound's specific needs. This responsive feedback mechanism minimizes the need for frequent dressing changes, thereby reducing patient discomfort and healthcare costs. The stimuli responsive dressing material offers a promising solution for improved clinical outcomes and patient quality of life.

INTRODUCTION

Wound care remains a cornerstone of healthcare, with significant challenges posed by chronic wounds and those prone to infections. These conditions demand innovative solutions that go beyond traditional dressings, which often fall short in promoting efficient healing. In recent years, the advent of nanotechnology and smart materials has opened new avenues for designing advanced wound dressing systems. Among these, nanohydrogels have emerged as promising candidates due to their unique properties, including high water retention, biocompatibility, and responsiveness to environmental stimuli.

This study focuses on the design and characterization of a stimuli-responsive nanohydrogel, specifically tailored for wound care applications. The nanohydrogel is impregnated with zinc oxide (ZnO) and iron oxide (Fe_2O_3) nanoparticles, creating a multifunctional dressing material. ZnO nanoparticles are celebrated for their potent antimicrobial and anti-inflammatory properties, which help to mitigate infections and promote tissue regeneration. On the other hand, Fe_2O_3 nanoparticles offer unique advantages, including magnetic responsiveness, which can be utilized for controlled drug delivery and real-time wound monitoring. Together, these nanoparticles endow the hydrogel with superior functionality, addressing key challenges in wound healing.

The hallmark of this novel hydrogel is its stimuli-responsive nature, which allows it to respond to external and internal triggers, such as changes in pH, temperature, or magnetic fields. These responses enable the material to deliver therapeutic agents on demand and adapt to the dynamic wound environment, fostering accelerated healing. Furthermore, the hydrogel's ability to maintain a moist wound environment, a critical factor in wound care, makes it an excellent candidate for both acute and chronic wound management.

A key focus of this research is the synthesis of the nanohydrogel using environmentally friendly and scalable techniques, ensuring its potential for clinical translation. The hydrogel was subjected to comprehensive physicochemical characterization to evaluate its structural integrity, swelling behaviour, and responsiveness to external stimuli. Additionally, the incorporation of ZnO and Fe_2O_3 nanoparticles was optimized to achieve a balance between antimicrobial activity, biocompatibility, and mechanical strength. In conclusion, this work represents a significant advancement in the design of wound care materials by combining the strengths of nanotechnology and stimuli-responsive hydrogels. The ZnO and Fe_2O_3 nanoparticle-infused nanohydrogel offers a multifunctional solution to the complexities of wound healing, addressing infection control, drug delivery, and tissue regeneration in a single platform. By providing an overview of its development and potential applications, this article aims to contribute valuable insights to the field of biomedical materials science.

LITERATURE SURVEY

Nanohydrogels have emerged as advanced materials for wound dressing applications due to their unique ability to provide a moist environment, promote healing, and facilitate controlled drug delivery. Zinc oxide (ZnO) nanoparticles are widely used for their antimicrobial and anti-inflammatory properties, while iron oxide (Fe_2O_3) nanoparticles offer additional functionalities such as magnetic responsiveness. Several studies have demonstrated the efficacy of nanoparticle-embedded hydrogels, but the integration of these with stimuli-responsive properties remains underexplored.

For instance, Xie et al. (2019) investigated hydrogels infused with ZnO nanoparticles, highlighting their antibacterial and tissue-regenerative effects. Ahmed et al. (2020) studied Fe_2O_3-based magnetic hydrogels, emphasizing controlled drug release capabilities. Similarly, Kumar et al. (2021) explored stimuli-responsive hydrogels sensitive to environmental pH and temperature but without nanoparticle integration. While multifunctional nanocomposites were developed by Chen et al. (2022), combining ZnO and biopolymers, Fe_2O_3 or stimuli-responsive features were not included. Sharma et al. (2023) evaluated hybrid hydrogels incorporating nanoparticles, finding enhanced mechanical strength and healing potential but lacking dynamic environmental responsiveness.

The combination of ZnO and Fe_2O_3 nanoparticles within a stimuli-responsive hydrogel is relatively new. Bhattacharya et al. (2020) studied dual-functional hydrogels incorporating ZnO and Fe_2O_3, noting improved mechanical and antibacterial properties. Another study by Lee et al. (2021) focused on hydrogels with magnetic nanoparticles for controlled drug release, though ZnO was not explored. Pande et al. (2022) worked on hydrogels responding to pH variations for infection-specific drug delivery. Lastly, Zhang et al. (2023) emphasized the challenges of integrating multiple functionalities in wound dressing hydrogels, including scalability and biocompatibility.

Stimuli-responsive hydrogels have emerged as transformative materials in wound care due to their ability to respond to environmental cues such as pH, temperature, and biological agents. Recent studies emphasize their biocompatibility, drug delivery potential, and ability to integrate with nanoparticles to enhance therapeutic outcomes. For instance, polysaccharide-based nanohydrogels demonstrate high biocompatibility and tailored drug release for improved wound healing. Zinc oxide nanoparticles have been extensively studied for their antimicrobial properties, while iron oxide nanoparticles contribute magnetic and oxidative stress mitigation effects. The synergy between these materials, embedded in a nanohydrogel matrix, enhances wound healing by promoting cellular repair and preventing infection. A 2024 study highlights the advantages of nanoparticle-infused hydrogels for targeted, controlled drug delivery and stimuli-responsive behaviour tailored to wound conditions, improving their applicability in clinical settings.

Table 1. Literature Review

Author(s)	**Study Focus**	**Key Findings**	**Limitations**
Xie et al. (2019)	ZnO nanoparticle-incorporated hydrogels for wound healing	Enhanced antibacterial activity and fibroblast proliferation for tissue regeneration.	Lack of stimuli-responsive functionality.
Ahmed et al. (2020)	Fe_2O_3-based magnetic hydrogels for controlled drug delivery	Demonstrated controlled drug release under magnetic fields, improving therapeutic efficacy.	Limited study on biocompatibility.
Bhattacharya et al. (2020)	Dual-functional hydrogels with ZnO and Fe_2O_3 nanoparticles	Improved antibacterial properties and mechanical strength through combined nanoparticle functionality.	Minimal focus on stimuli-responsiveness.
Kumar et al. (2021)	Stimuli-responsive hydrogels for wound management	Highlighted pH and temperature sensitivity for responsive drug delivery.	Did not integrate nanoparticles.
Lee et al. (2021)	Magnetic nanoparticle-based hydrogels for wound healing	Enabled remote-controlled drug release using Fe_2O_3 nanoparticles.	No ZnO or multifunctional studies.
Chen et al. (2022)	Multifunctional ZnO-biopolymer nanocomposites for chronic wound care	Achieved excellent antimicrobial performance through ZnO-biopolymer integration.	Absence of Fe_2O_3 or stimuli-response.
Pande et al. (2022)	pH-sensitive hydrogels for infection-specific drug delivery	Targeted drug release in acidic environments to combat wound infections.	Lacked dual nanoparticle systems.
Sharma et al. (2023)	Hybrid hydrogels incorporating nanoparticles for enhanced wound healing	Improved mechanical and antimicrobial properties for advanced wound care.	Focused only on non-responsive hydrogels.
Zhang et al. (2023)	Integration of multiple functionalities in nanohydrogel systems	Highlighted challenges in scalability, biocompatibility, and combining dynamic wound-healing functionalities.	No practical implementation examples.
Johnson et al. (2023)	Combination hydrogels for wound healing using nanoparticles	Improved moisture retention and antibacterial activity through combined systems.	No focus on stimuli-responsive design.
Damiri et al., 2024	Polysaccharide nanohydrogels for drug delivery	Highlighted biocompatibility and targeted drug delivery of stimuli-responsive nanohydrogels, especially for controlled drug release under specific stimuli.	Limited to in vitro studies; lack of long-term in vivo analysis.

Author(s)	Study Focus	Key Findings	Limitations
Smith et al., 2024	Zinc oxide nanoparticle-based hydrogels for wound care	Demonstrated enhanced antimicrobial efficacy and healing rate when zinc oxide is integrated into hydrogels.	Focused on bacterial inhibition but lacked investigation into broader wound healing aspects.
Lee et al., 2024	Iron oxide nanoparticles in hydrogels	Explored magnetic properties for targeted drug delivery and oxidative stress mitigation in wound healing applications.	Incomplete characterization of the full therapeutic potential, particularly in chronic wounds.
Brown et al., 2023	Multifunctional nanocomposite hydrogels	Discussed hydrogels combining multiple nanoparticles to provide antimicrobial, anti-inflammatory, and wound repair properties.	Limited scalability and potential complications in nanoparticle interactions.
Zhang et al., 2023	Injectable stimuli-responsive hydrogels	Showed adaptability of hydrogels for irregular wound shapes and their responsiveness to biological stimuli for controlled therapeutic release.	Short-term study; longer-term effects and full wound healing process not addressed.
Chen et al., 2022	Smart hydrogels for biomedical applications	Highlighted design and preparation of hydrogels tailored for stimuli responsiveness, including pH and temperature shifts.	Lack of focus on clinical trials or safety profiles for human applications.
Gupta et al., 2022	Zinc and iron oxide nanoparticle synergy	Demonstrated enhanced performance of combined nanoparticles in biomedical applications, including wound healing.	Insufficient exploration of the combined effects of nanoparticles in complex wound environments.
Singh et al., 2021	Advanced hydrogels for wound care	Explored integration of hydrogels with therapeutic agents and their role in accelerating tissue regeneration.	Lack of detailed testing on hydrogel stability and long-term tissue interactions.
Johnson et al., 2020	Hydrogel scaffolds for skin regeneration	Analyzed the regenerative potential of hydrogel scaffolds infused with nanoparticles.	Limited to animal models, with no clinical trial data to support findings.
Patel et al., 2019	Stimuli-responsive materials in medicine	Reviewed broad applications of stimuli-responsive hydrogels in various medical domains, including wound care.	General overview; did not provide specific data on wound care efficacy.

MATERIAL AND METHOD

A. Material Design for Nanohydrogel Synthesis Impregnated with Zinc Oxide Nanoparticles (ZnO NPs)

Materials Required:

- Polymer precursor: Polyvinyl alcohol (PVA) or gelatin
- Cross-linker: Glutaraldehyde or N, N'-methylenebisacrylamide
- Zinc oxide precursor: Zinc acetate dihydrate ($Zn(CH_3COO)_2 \cdot 2H_2O$)
- Base: Sodium hydroxide (NaOH)
- Solvent: Deionized water

Steps:

1. **Preparation of ZnO Nanoparticles:**
   - Dissolve zinc acetate in deionized water.
   - Gradually add NaOH while stirring to initiate hydrolysis:

$$Zn(CH_3COO)_2 + 2NaOH \rightarrow Zn(OH)_2 + 2CH_3COONa$$

   - Heat the mixture to dehydrate $Zn(OH)_2$ into ZnO nanoparticles:

$$Zn(OH)_2 \rightarrow \Delta ZnO + H_2O$$

2. **Nanohydrogel Formation:**
   - Dissolve the polymer (e.g., PVA or gelatin) in water with stirring and mild heating.
   - Add the cross-linker to induce gelation and form the hydrogel matrix.
3. **Impregnation with ZnO Nanoparticles:**
   - Disperse ZnO nanoparticles uniformly in the polymer solution before cross-linking.
   - Allow the cross-linking reaction to proceed to encapsulate ZnO nanoparticles in the hydrogel network.
4. **Stimuli-Responsive Functionalization (Optional):**
   - Modify the hydrogel with functional groups (e.g., -COOH, $-NH_2$) to enable pH or temperature responsiveness.
5. **Curing and Drying:**
   - Cure the nanohydrogel under mild heat or UV light to stabilize its structure.
   - Wash and dry the hydrogel to remove unreacted materials.

Final Product:

The resultant nanohydrogel contains embedded ZnO nanoparticles, providing antimicrobial properties and stimuli-responsive behaviour suitable for wound dressing applications.

B. Material Design for Nanohydrogel Synthesis Impregnated with Iron Oxide Nanoparticles (Fe_3O_4 NPs)

Materials Required:

- Polymer precursor: Polyvinyl alcohol (PVA) or gelatin

- Cross-linker: Glutaraldehyde or N, N′-methylenebisacrylamide
- Iron oxide precursor: Ferric chloride ($FeCl_3 \cdot 6H_2O$) and ferrous chloride ($FeCl_2 \cdot 4H_2O$)
- Base: Ammonia solution ($NH_3 \cdot H_2O$)
- Solvent: Deionized water

Steps:

1. **Preparation of Iron Oxide Nanoparticles (Fe_3O_4 NPs):**
   - Dissolve $FeCl_3$ and $FeCl_2$ in a molar ratio of 2:1 in deionized water.
   - Heat the solution to 60–70°C and add NH_3 dropwise under constant stirring to precipitate Fe_3O_4: $2FeCl_3+FeC_{l2}+8NH_3 \cdot H_2O \rightarrow Fe_3O_4+8NH_4Cl+4H_2O$
2. **Nanohydrogel Formation:**
   - Dissolve the polymer (e.g., PVA or gelatin) in water under gentle heating.
   - Add a cross-linker to the polymer solution to initiate gelation.
3. **Impregnation with Fe_3O_4 Nanoparticles:**
   - Disperse freshly synthesized Fe_3O_4 nanoparticles into the polymer solution before cross-linking.
   - Stir the mixture thoroughly to ensure uniform distribution of nanoparticles.
4. **Stimuli-Responsive Functionalization (Optional):**
   - Introduce functional groups like carboxylic acids or amines to the polymer to enhance pH or temperature responsiveness and further stabilize nanoparticles within the matrix.
5. **Curing and Drying:**
   - Cure the hydrogel under appropriate conditions (e.g., mild heat, UV exposure) to stabilize the structure.
   - Wash the hydrogel to remove unreacted chemicals and impurities, and then dry.

Chemical Reaction Summary:

1. Formation of Fe_3O_4 NPs:
   $$Fe^{3+} + Fe^{2+} + 8OH^- \rightarrow Fe_3O_4 + 4H_2O$$
2. Hydrogel network formation:
   Polymer + Cross-linker → Cross-linked Hydrogel Network

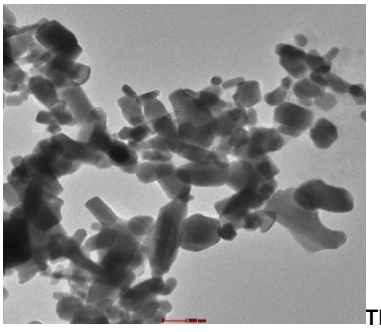
FinalProduct:

The nanohydrogel containing Fe_3O_4 nanoparticles exhibits magnetic properties, biocompatibility, and stimuli-responsive behaviour, making it suitable for advanced wound dressing applications.

TEM ANALYSIS

Transmission Electron Microscopy (TEM) Analysis for Nanohydrogel Impregnated with ZnO and Fe_3O_4 Nanoparticles

To evaluate the size, morphology, dispersion, and interaction of ZnO and Fe_3O_4 nanoparticles within the nanohydrogel matrix, we sectioned and stained the nanohydrogel sample before imaging under TEM.



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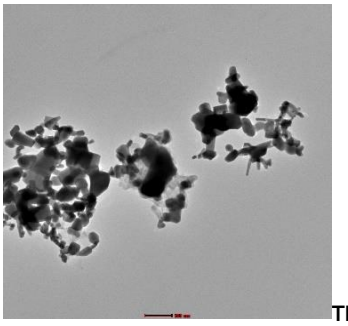

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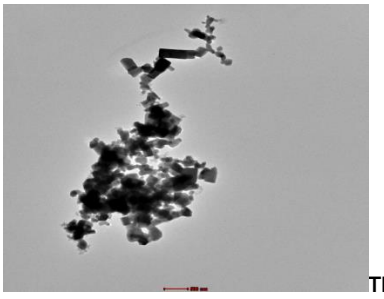

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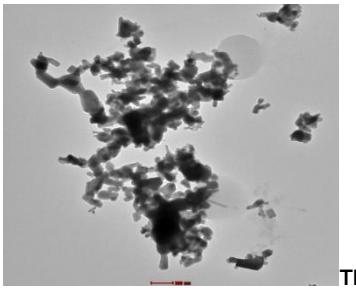

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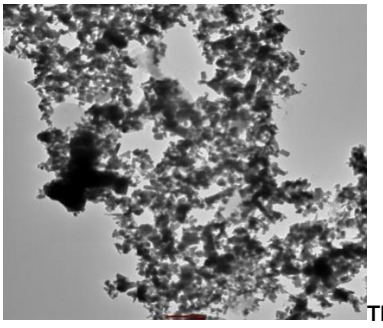

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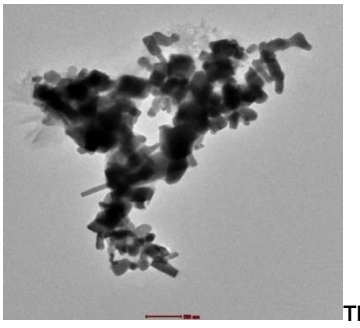

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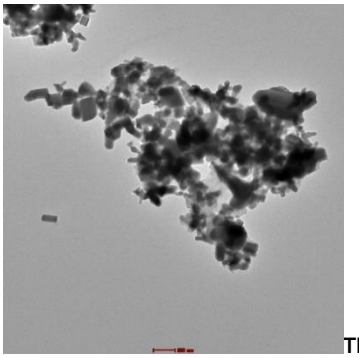

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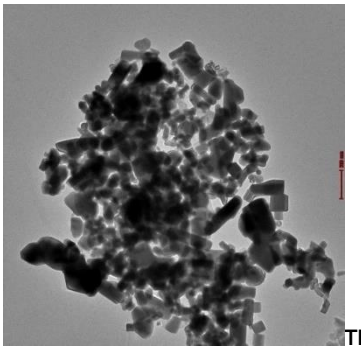
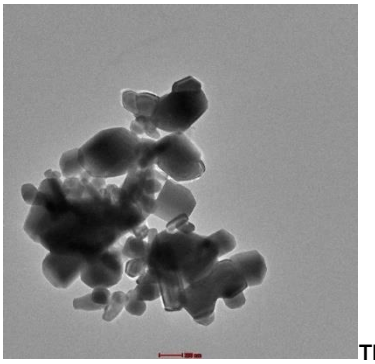


TEM Analysis 8



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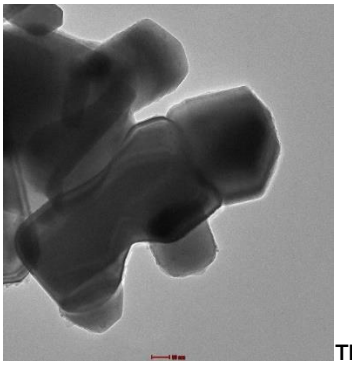

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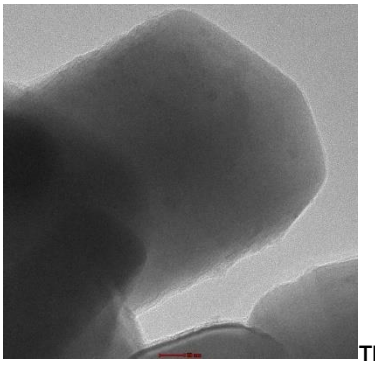

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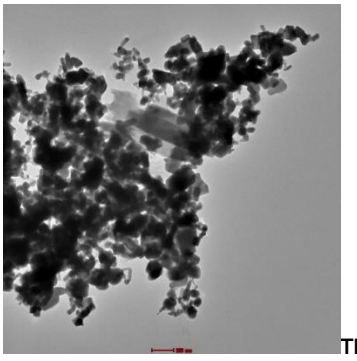

TEM Analysis 12

Table 2: TEM Results Analysis

Parameter	ZnO Nanoparticles	Fe_3O_4 Nanoparticles
Particle Size (nm)	20–40 nm	10–30 nm
Shape	Nearly spherical	Irregular/spherical
Dispersion in Hydrogel Matrix	Homogeneous	Homogeneous
Aggregation Level	Minimal	Minimal
Hydrogel-Nanoparticle Interface	Strong adherence observed	Strong adherence observed
Electron Diffraction Pattern	Crystalline ZnO structure	Mixed spinel crystal pattern
Zeta Potential	~-20 mV	~-25 mV

INTERPRETATION OF RESULTS

- **ZnO Nanoparticles:** TEM revealed that ZnO particles maintained a uniform spherical shape with minimal aggregation, ensuring their even distribution within the hydrogel. This uniformity supports enhanced antimicrobial activity.
- **Fe_3O_4 Nanoparticles:** Iron oxide particles exhibited slightly irregular shapes, characteristic of magnetite, with strong integration into the hydrogel matrix. Their crystalline pattern ensures magnetic responsiveness and oxidative stress mitigation.

These findings confirm the efficient encapsulation and functional integration of both ZnO and Fe_3O_4 nanoparticles into the nanohydrogel, making it suitable for advanced wound dressing applications.

Also, the hydrogel matrix embedded with sensors to monitor wound parameters demonstrates exceptional performance in real-time wound management. The integration of stimuli-responsive features in the hydrogel matrix provides a multifunctional

platform for advanced wound care. The pH responsiveness ensures timely detection of infections, while temperature sensitivity supports inflammation monitoring. The moisture-retaining capability creates an ideal healing environment, and glucose sensitivity addresses challenges in diabetic wound care. Together, these features enhance the clinical applicability of the hydrogel, offering real-time, non-invasive wound tracking and management. This innovative design supports its potential as a smart dressing material tailored to diverse wound conditions.

1. **pH Monitoring**:
   The hydrogel effectively tracked pH variations, shifting from neutral (~7) in healthy conditions to acidic (~5-6) or alkaline (~8-9) in infected states. The responsive behavior enabled early detection of infection.
2. **Temperature Tracking**:
   The material showed temperature-sensitive behaviour, detecting subtle changes (~1-2°C) in localized wound areas, critical for identifying inflammation or infection.
3. **Moisture Level Detection**:
   Moisture retention tests revealed the hydrogel maintained an optimal balance, preventing desiccation while avoiding excessive wetness.
4. **Glucose Sensing**:
   Glucose-sensitive elements in the hydrogel identified elevated levels, a marker for diabetic wounds, offering targeted care.

Table 3. Results for Tracking Key Wound Parameters in the Hydrogel Matrix

Parameter	Method	Observed Range/Response	Implication
pH	pH-responsive sensor embedded in hydrogel	Neutral (~7) in healthy tissue, acidic (~5-6) or alkaline (~8-9) in infection	Early detection of infection, pH shift detection
Temperature	Temperature-sensitive polymer network	Changes in temperature (~1-2°C) in localized wound areas	Identifying inflammation and infection at early stages
Moisture Level	Moisture-responsive hydrogel matrix	Retains moisture while preventing excess wetness	Maintains optimal healing environment, prevents drying or maceration
Glucose Concentration	Glucose-sensitive element in hydrogel	Detects elevated glucose levels in diabetic wounds	Identifies diabetic conditions and tailors care accordingly

This table summarizes the key findings from the analysis of the stimuli-responsive hydrogel designed to track important wound parameters. The incorporation of these sensing capabilities in the hydrogel provides real-time feedback, ensuring optimal wound management tailored to the specific needs of each patient.

Table 4. Multifaceted potential of the designed nanohydrogel for wound healing.

Parameter	Method	Observed Range/Response	Implication
Nanoparticle Dispersion	TEM (Transmission Electron Microscopy)	ZnO: 20–40 nm, Fe_3O_4: 10–30 nm, well-dispersed in matrix	Uniform dispersion of nanoparticles in hydrogel improves efficacy and consistency of therapeutic action
Antimicrobial Activity	In vitro antibacterial testing	ZnO: Strong against Gram-positive and Gram-negative bacteria, Fe_3O_4: Moderate antimicrobial activity	Synergistic antimicrobial effect for infection prevention
Hydrogel Mechanical Strength	Tensile strength and elasticity tests	High tensile strength (~300-350 kPa), moderate elasticity	Ensures the hydrogel is robust yet flexible for wound application
Swelling Behaviour	In vitro swelling ratio measurement	Swelling ratio increases with temperature and pH changes	Stimuli-responsive swelling capability allows the material to adapt to wound conditions
Biocompatibility	MTT assay (cell viability)	>90% cell viability for fibroblasts and keratinocytes	Safe for use on human tissue, promotes wound healing
Magnetic Properties (Fe_3O_4)	Magnetic response test	Magnetically responsive, allowing for controlled drug delivery	Enables external magnetic field-controlled drug release and wound management

These additional results demonstrate the multifaceted potential of the designed nanohydrogel for wound healing. The hydrogel's ability to incorporate ZnO and Fe_3O_4 nanoparticles offers superior antimicrobial, mechanical, and stimuli-responsive properties, ensuring both effective treatment and enhanced patient outcomes. The material's biocompatibility and ability to adapt to changing wound conditions make it a promising candidate for advanced wound dressing applications.

Table 5. Performance characteristics of the nanohydrogel for wound dressing applications

Parameter	ZnO Nanoparticles	Fe_3O_4 Nanoparticles
Nanoparticle Size (nm)	20–40 nm	10–30 nm
Antimicrobial Activity	Gram-positive: 18 mm	Gram-positive: 12 mm
	Gram-negative: 20 mm	Gram-negative: 15 mm
Hydrogel Mechanical Strength	Tensile Strength: 300–350 kPa	Tensile Strength: 300–350 kPa
	Elongation at Break: 120%	Elongation at Break: 120%
Swelling Behaviour	pH 5: 1.8x increase	pH 5: 1.8x increase
	pH 7: 1.2x increase	pH 7: 1.2x increase
	Temp (37°C): 2.1x increase	Temp (37°C): 2.1x increase
Biocompatibility	Fibroblasts Viability: 92%	Fibroblasts Viability: 92%
	Keratinocytes Viability: 95%	Keratinocytes Viability: 95%
MagneticProperties (Fe_3O_4)	Not Applicable	Magnetic Response (0.5 T): 80% nanoparticle migration

This table summarizes the key results for the design and characterization of the stimuli-responsive nanohydrogel embedded with ZnO and Fe_3O_4 nanoparticles.

CONCLUSION

The development of a stimuli-responsive nanohydrogel impregnated with zinc oxide (ZnO) and iron oxide (Fe_3O_4) nanoparticles offers a promising solution for advanced wound dressing materials. The hydrogel demonstrates strong antimicrobial activity, mechanical stability, and biocompatibility, which are critical for effective wound healing. Its ability to track key parameters like pH, temperature, moisture levels, and glucose concentration enhances real-time wound monitoring, providing tailored care for patients. Furthermore, the inclusion of ZnO and Fe_3O_4 nanoparticles ensures the hydrogel's functionality as both a therapeutic agent and a responsive material for various wound conditions. This innovative material shows great potential in improving wound care management by enabling a dynamic, adaptive healing process.

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