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ENGINEERING POLYOXAZOLINE-BASED NANO-HYDROGELS FOR MULTIFUNCTIONAL WOUND CARE: MOLECULAR ARCHITECTURE, DRUG DELIVERY, HEALING MECHANISMS AND TRANSLATIONAL CHALLENGES

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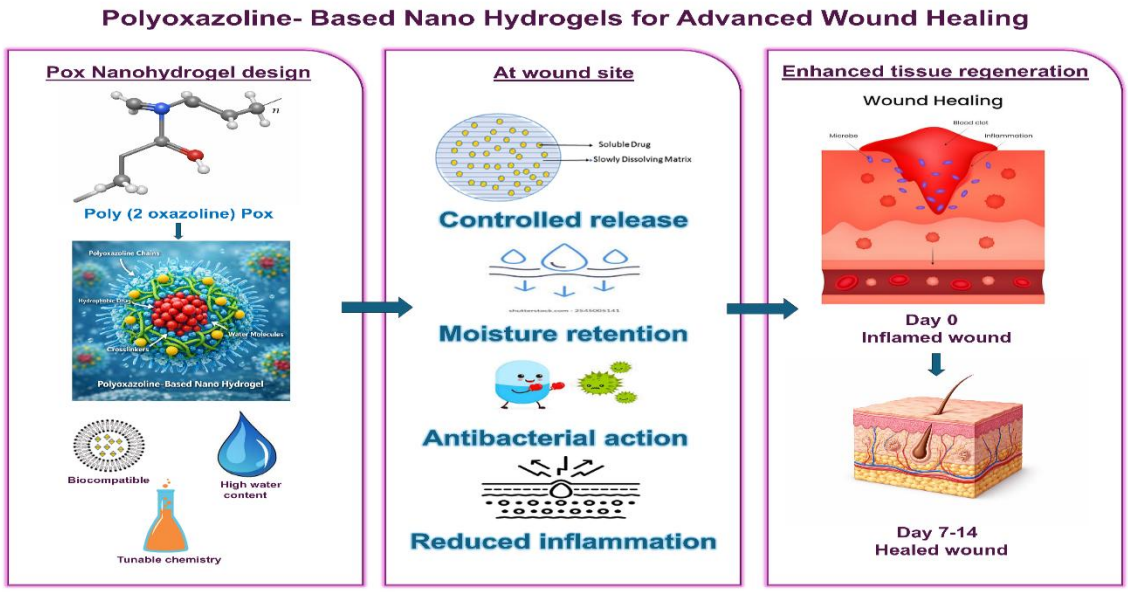
ABSTRACT

Effective wound management remains a significant clinical challenge, particularly in chronic and non-healing wounds where infection, prolonged inflammation and impaired tissue regeneration hinder recovery. Advanced biomaterials capable of providing a moist environment, controlled drug delivery and biological support are increasingly explored to address these limitations. Among emerging candidates, polyoxazoline-based nano hydrogels have gained attention due to their unique physicochemical versatility, excellent biocompatibility and structural tunability. These polymers exhibit adjustable hydrophilicity, thermal responsiveness and low protein adsorption, making them suitable for biomedical applications. When engineered at the nanoscale, polyoxazoline hydrogels demonstrate enhanced surface area, improved cellular interaction and efficient encapsulation of therapeutic agents. This review examines the synthesis strategies, structural characteristics and functional modifications of polyoxazoline nano hydrogels relevant to wound healing. Emphasis is placed on their role in promoting haemostasis, modulating inflammation, accelerating re-epithelialization and supporting extracellular matrix remodelling. The potential of these nano-structured systems for stimuli-responsive drug release and infection control is also discussed. Furthermore, current preclinical findings, translational considerations and existing challenges related to scalability, regulatory approval and long-term safety are critically analysed. By integrating material science principles with wound biology, this review highlights how polyoxazoline-based nano hydrogels represent promising platform for next-generation wound dressings and regenerative therapies.

KEYWORDS: Polyoxazoline; Nano hydrogels; Smart biomaterials; Tissue regeneration.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Chronic and acute wounds remain a major clinical challenge due to delayed healing, infection risk and high recurrence rates, particularly in patients with diabetes, burns or vascular disorders[1]. In this context, polyoxazoline-based nano-hydrogels have emerged as promising candidates owing to their exceptional biocompatibility, structural versatility and tuneable physicochemical properties[2]. Polyoxazolines offer a synthetic alternative to conventional polymers, enabling precise control over hydrophilicity, degradation behaviour and functional group incorporation[3]. When engineered at the nanoscale, these hydrogels provide a moist wound environment, protect bioactive agents and facilitate controlled release of therapeutics such as growth factors, antimicrobials or antioxidants. Their nanosized architecture further enhances tissue penetration and cellular interactions, promoting angiogenesis and re-epithelialization[4].

Acute wounds, such as those resulting from surgery, trauma or thermal injury, generally heal through a coordinated sequence of inflammation, tissue formation and remodelling; however, complications including infection, ischemia and excessive inflammatory responses can disrupt this process and delay closure[5]. Chronic wounds, including diabetic foot ulcers, pressure injuries and venous leg ulcers, fail to progress through normal healing stages and often persist for extended periods[6]. The increasing prevalence of diabetes, vascular disorders, aging populations and lifestyle-related comorbidities has contributed to a rising incidence of non-healing wounds, particularly in vulnerable patient groups[7]. Conventional wound dressings, including gauze, films, foams and hydrocolloids, remain widely used in routine clinical practice but exhibit several inherent limitations when applied to complex or chronic wounds[8]. Most traditional dressings function primarily as passive barriers, offering mechanical protection and exudate absorption without actively supporting the biological processes required for tissue regeneration[9]. Dry or adhesive materials may adhere to the wound bed, causing secondary injury and discomfort during dressing changes, which can further delay healing[10]. Additionally, many conventional dressings fail to consistently maintain an optimal moist environment, a critical factor for cell migration, angiogenesis and re-epithelialization[11]. Poor moisture regulation can result in wound desiccation or maceration of surrounding tissue, both of which increase infection risk. Furthermore, conventional dressings lack responsiveness to dynamic changes within the wound microenvironment, such as shifts in pH, enzymatic activity or microbial load. Although some advanced dressings incorporate antimicrobial agents, their release is often uncontrolled, potentially leading to reduced efficacy or cytotoxic effects on healthy cells[12].

The limitations of traditional wound care approaches have driven interest in advanced biomaterial-based therapies, particularly nano-hydrogel systems, as next-generation wound dressings[13]. Nano-hydrogels are three-dimensional polymeric networks capable of retaining high water content while operating at the nanoscale, enabling intimate interaction with the wound surface[14]. Their hydrated structure supports a moist healing environment, facilitates oxygen diffusion and protects newly formed tissue from external contaminants[15]. The nanoscale architecture enhances surface area and cellular interactions, promoting fibroblast activity, angiogenesis and epithelial regeneration. Fig.1 Importantly, nano-hydrogels can be engineered to encapsulate and release therapeutic agents in a controlled and sustained manner, allowing localized delivery of antimicrobials, anti-inflammatory compounds and regenerative biomolecules[16]. Their physicochemical properties can be tailored to respond to wound-specific conditions, enabling adaptive treatment of complex wounds[17]. Collectively, nano-hydrogel-based wound therapies represent a shift from passive wound coverage toward multifunctional, bioactive platforms capable of addressing the diverse biological challenges[18].

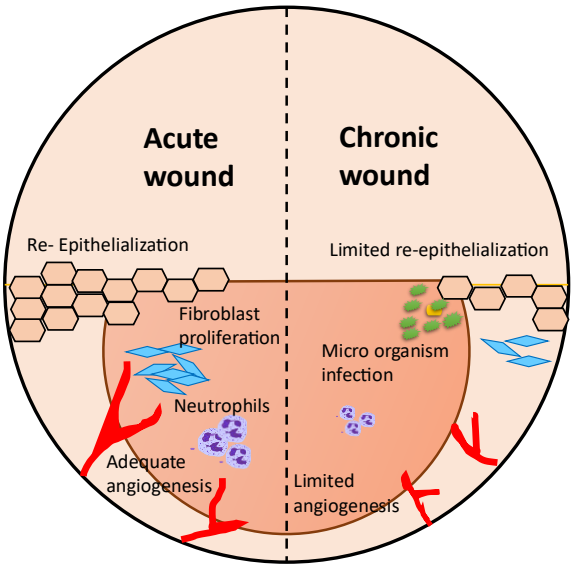


Fig. 1. Schematic overview of normal vs. impaired wound healing

The rationale for nano-hydrogel-based wound therapies also lies in their adaptability and tunability [16]. This responsive behaviour is particularly advantageous for chronic wounds, where prolonged inflammation and

microbial colonization require dynamic treatment approaches[19]. Additionally, nano-hydrogels exhibit favourable biocompatibility and can be formulated to degrade gradually into non-toxic byproducts, reducing the need for frequent dressing changes and minimizing patient discomfort[14]. Their injectable or sprayable forms further allow easy application to irregular wound surfaces, ensuring uniform coverage and improved patient compliance. Collectively, nano-hydrogel-based wound therapies represent a paradigm shift from passive wound coverage to active, multifunctional treatment platforms[20]. By simultaneously addressing moisture balance, infection control, inflammation regulation and tissue regeneration, these advanced systems offer a promising solution to overcome the clinical challenges associated with acute and chronic wounds and pave the way for more effective and personalized wound care strategies[21].

2. Polyoxazoline Polymers: Fundamentals and Biomedical Relevance

Polyoxazoline polymers have gained increasing attention in biomedical research due to their well-defined chemistry, structural versatility and favourable biological performance[22]. These polymers are synthesized from 2-oxazoline monomers through controlled ring-opening polymerization, a process that enables precise regulation of molecular weight, polymer architecture and functional group placement[3]. The living nature of this polymerization strategy allows the formation of linear, block, gradient and star-shaped polymers with narrow molecular weight distributions, making polyoxazolines highly adaptable for advanced biomedical applications[22]. By varying the substituents on the oxazoline ring, polymers with distinct hydrophilic or hydrophobic characteristics can be obtained, offering fine control over solubility and intermolecular interactions[23]. This synthetic flexibility distinguishes polyoxazolines from many conventional polymers and supports their integration into complex delivery systems, surface coatings and hydrogel networks. From a physicochemical perspective, polyoxazolines exhibit a combination of properties that are particularly advantageous for medical use[24].

2.1. Chemical Structure and Polymerization Strategies

Polyoxazolines are synthetic polymers derived from 2-oxazoline monomers, characterized by a five-membered heterocyclic ring containing both nitrogen and oxygen atoms[25]. Their polymer backbone resembles that of peptides, which contributes to their favourable biological interactions. Polyoxazolines are typically synthesized through cationic ring-opening polymerization, a controlled process that allows precise regulation of molecular weight, chain length and polymer architecture[26]. This living polymerization approach enables the fabrication of linear, block and star-shaped polymers with narrow dispersity. By altering monomer side chains and reaction conditions, polymers with tailored hydrophilicity, functionality and responsiveness can be produced, making polyoxazolines highly versatile for biomedical material design[22].

2.2. Tenable Physicochemical Properties of Polyoxazolines

Polyoxazolines display high chemical stability under physiological conditions while remaining amenable to functionalization with bioactive ligands, drugs or crosslinking agents[27]. These features enable the design of materials with tailored swelling behaviour, mechanical strength and degradation profiles, which are essential parameters for applications such as drug delivery, tissue engineering and wound healing[28]. The ability to fine-tune polymer–water interactions also support the formation of soft, hydrated matrices that can maintain moisture balance and support cellular activity[29].

2.3. Biocompatibility and Immunological Profile

The biocompatibility and immunological profile of polyoxazolines, which has contributed significantly to their growing biomedical relevance[30]. Numerous studies have demonstrated that polyoxazoline-based materials exhibit low cytotoxicity and minimal interference with normal cellular functions[31]. Their non-ionic nature and hydrophilic surface characteristics reduce undesirable interactions with immune cells, resulting in limited inflammatory responses upon implantation or topical application[32]. Compared to some widely used synthetic polymers, polyoxazolines show reduced complement activation and lower potential for inducing hypersensitivity reactions[30]. This immunological neutrality makes them suitable for repeated or long-term exposure, an important consideration in chronic wound management and sustained therapeutic delivery. Furthermore, polyoxazolines have been explored as alternatives to polyethylene glycol due to their comparable stealth behaviour and improved stability under oxidative conditions[33]. Collectively, the controlled polymerization strategies, tuneable physicochemical characteristics and favourable biocompatibility profile of polyoxazolines establish them as a versatile and reliable polymer platform for biomedical applications, particularly in the development of advanced hydrogel systems designed to interact safely and effectively with biological tissues[34].

3. Nano-Hydrogels in Wound Healing

Nano-hydrogels have emerged as a promising class of advanced biomaterials for wound healing due to their ability to integrate structural support with biological functionality at the nanoscale[14]. Wound repair is a highly dynamic process involving inflammation control, cell migration, angiogenesis, extracellular matrix deposition and tissue remodelling, all of which are influenced by the local microenvironment[35]. Traditional materials often fail to address these interconnected events simultaneously. Nano-hydrogels, defined as three-dimensional polymeric networks with dimensions typically below a few hundred nanometres, are specifically designed to interact with wound tissue at a cellular and molecular level. Their design is guided by key principles that balance mechanical integrity, hydration capacity, biocompatibility and responsiveness to physiological conditions[36]. At the core of nano-hydrogel design is the selection of polymer systems that can form stable yet flexible networks capable of retaining large amounts of water. Crosslinking strategies, whether physical or chemical, are carefully chosen to

achieve controlled swelling, adequate mechanical strength and predictable degradation behaviour[37]. The nanoscale size further requires precise control over particle uniformity, surface chemistry and porosity to ensure consistent performance and safe biological interactions[38].

3.1. Design Principles of Nano-Hydrogels

An important design consideration for nano-hydrogels in wound healing is their ability to maintain a moist environment while allowing oxygen diffusion and waste removal[39]. Adequate hydration supports keratinocyte migration, fibroblast proliferation and collagen synthesis, all of which are essential for effective wound closure[40]. Nano-hydrogels are also engineered to be highly porous, enabling efficient exchange of nutrients and gases while acting as a protective barrier against external contaminants[41]. Surface functionalization plays a crucial role in enhancing cellular adhesion and modulating biological responses. By incorporating functional groups or bioactive motifs, nano-hydrogels can promote cell attachment, regulate inflammatory signalling and support angiogenic processes[42]. In addition, many nano-hydrogel systems are designed to encapsulate therapeutic agents such as antimicrobial compounds, antioxidants or growth-promoting molecules.Fig.2 Controlled and sustained release from the hydrogel matrix ensures localized treatment, reduces systemic exposure and minimizes the need for frequent dressing changes[43].

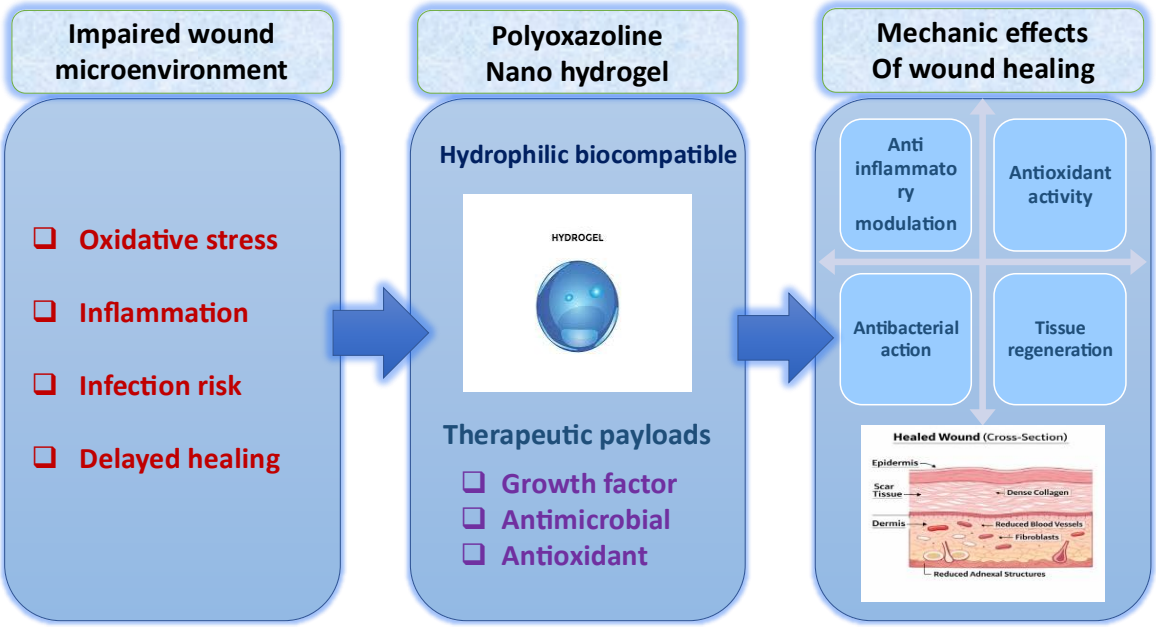


Fig. 2. Mechanistic role of polyoxazoline nano-hydrogel in wound healing.

3.2. Advantages of Nanoscale Hydrogel Architectures

The nanoscale architecture of these hydrogels offers several advantages over larger, bulk hydrogel systems[44]. One of the most significant benefits is the increased surface area-to-volume ratio, which enhances interaction with wound tissue and surrounding cells[45]. This feature allows nano-hydrogels to respond more rapidly to environmental cues such as changes in pH, enzymatic activity or oxidative stress commonly present in chronic wounds[46]. Their small size also facilitates deeper penetration into irregular wound surfaces and microcavities, ensuring more uniform coverage and effective contact with damaged tissue. This is particularly beneficial in complex wounds where uneven geometry can limit the performance of conventional materials[47]. Furthermore, nano-hydrogels can be formulated as injectable, sprayable or spreadable systems, improving ease of application and patient comfort. Their ability to conform to wound contours reduces dead space, lowers infection risk and enhances therapeutic efficiency[48].

Another key advantage of nanoscale hydrogel systems is their enhanced capacity for multifunctionality. Nano-hydrogels can be engineered to perform multiple roles simultaneously, including moisture retention, infection control, inflammation modulation and tissue regeneration[49]. This multifunctional nature is critical in chronic wounds, where prolonged inflammation and microbial colonization coexist with impaired cellular activity[50]. By delivering bioactive agents in a controlled manner, nano-hydrogels can help restore balance within the wound microenvironment and support progression through the normal stages of healing[51]. Additionally, their tuneable degradation rates allow the material to gradually break down as new tissue forms, reducing the need for mechanical removal and minimizing trauma to regenerating tissue[52].

3.3. Comparison with Conventional Hydrogel Systems

When compared with conventional hydrogel systems, nano-hydrogels demonstrate clear advantages in terms of responsiveness, adaptability and biological interaction[53]. Conventional hydrogels, while effective in maintaining moisture and providing a protective barrier, are typically macroscopic structures with limited surface interaction and slower response to environmental changes[54]. Their bulk nature can restrict oxygen diffusion and reduce efficiency in delivering therapeutic agents uniformly across the wound bed. In contrast, nano-hydrogels

exhibit faster swelling and deswelling kinetics, improved drug-loading efficiency and more precise control over release profiles[55]. Conventional hydrogels may also suffer from poor mechanical stability or excessive rigidity, which can hinder cell migration and tissue integration. Nano-hydrogels, by virtue of their size and network design, can achieve a balance between softness and structural integrity that more closely resembles native tissue[56].

4. Fabrication of Polyoxazoline-Based Nano-Hydrogels

Polyoxazoline-based nano-hydrogels are fabricated through carefully designed synthetic and assembly strategies that integrate precise polymer chemistry with controlled network formation at the nanoscale. The fabrication process begins with the synthesis of polyoxazoline polymers, which are typically produced via controlled cationic ring-opening polymerization of 2-oxazoline monomers[57]. This polymerization approach enables accurate control over molecular weight, chain length and polymer architecture, which are critical parameters for hydrogel formation and performance[58]. By selecting appropriate monomers and reaction conditions, polyoxazolines with tailored hydrophilicity, thermal behaviour and functional group density can be obtained[59]. Post-polymerization functionalization further expands their versatility, allowing the introduction of reactive moieties such as hydroxyl, carboxyl, thiol or amine groups along the polymer backbone or at chain termini[60]. These functional groups serve as anchoring points for crosslinking reactions, bioactive molecule conjugation or surface modification, enabling the design of nano-hydrogels with application-specific properties. Functionalization strategies are typically designed to preserve polymer biocompatibility while enhancing responsiveness to physiological stimuli present in wound environments[61].

4.1. Crosslinking and Network Formation

Crosslinking and network formation represent a central step in converting functionalized polyoxazoline chains into stable nano-hydrogel systems[62]. Crosslinking can be achieved through physical or chemical mechanisms, each offering distinct advantages depending on the intended application[63]. Physical crosslinking relies on non-covalent interactions such as hydrogen bonding, hydrophobic association or ionic interactions, resulting in reversible and often stimuli-responsive networks. These systems are particularly attractive for wound healing, as they can adapt dynamically to changes in moisture, temperature or pH while minimizing the use of potentially toxic crosslinking agents[63]. Chemical crosslinking, in contrast, involves the formation of covalent bonds between polymer chains using crosslinkers or reactive functional groups. This approach yields mechanically robust and structurally stable nano-hydrogels with predictable swelling and degradation behaviour[64]. The density and type of crosslinks can be precisely adjusted to control mechanical strength, porosity and water retention, which are key factors influencing cell migration, nutrient diffusion and drug release[65]. Importantly, mild reaction conditions are often employed to ensure that the crosslinking process does not compromise the biological compatibility of the material or any encapsulated therapeutic agents[66].

The formation of nano-hydrogels requires additional control beyond conventional hydrogel fabrication, as network development must occur at the nanoscale. One widely used approach involves the preparation of pre-crosslinked polymer nanoparticles, followed by stabilization of the internal network structure[67]. Alternatively, nano-hydrogels can be formed through in situ crosslinking during nanoparticle generation, enabling simultaneous size control and network formation[68]. Emulsion-based techniques, nanoprecipitation and microfluidic methods are frequently employed to regulate particle size distribution and morphology[69]. These fabrication strategies allow the production of uniform nano-hydrogels with well-defined dimensions, which is essential for consistent biological interactions and reproducible therapeutic performance[70].

4.2. Self-Assembly and Nano structuring Approaches

Self-assembly and nano structuring approaches play a crucial role in the fabrication of polyoxazoline-based nano-hydrogels, particularly for systems designed to respond to environmental cues[71]. Amphiphilic polyoxazolines, which contain both hydrophilic and hydrophobic segments, can spontaneously self-assemble in aqueous environments to form nanoscale structures such as micelles or nanogels[72]. This self-assembly process is driven by thermodynamic minimization of free energy, leading to the formation of a hydrophobic core surrounded by a hydrated shell. Subsequent crosslinking of these assemblies stabilizes the structure, transforming them into permanent nano-hydrogels capable of retaining their architecture under physiological conditions[73]. Self-assembly offers a powerful route to fabricate nano-hydrogels without extensive processing steps, while also enabling efficient encapsulation of hydrophobic and hydrophilic therapeutic agents[74].

Nano structuring approaches further enhance the functional performance of polyoxazoline-based nano-hydrogels by enabling hierarchical organization and spatial control within the polymer network. By adjusting polymer composition, block length and assembly conditions, researchers can fine-tune particle size, surface charge and internal porosity[75]. These parameters directly influence cellular uptake, tissue interaction and release kinetics of loaded bioactive molecules[76]. In wound healing applications, nanostructured hydrogels can be engineered to release therapeutic agents in a sustained or stimuli-responsive manner, addressing challenges such as infection control, inflammation regulation and tissue regeneration[77]. Additionally, the soft and hydrated nature of polyoxazoline nano-hydrogels allows them to conform to irregular wound surfaces, improving contact with the wound bed and enhancing therapeutic efficacy[14].

5. Physicochemical Characteristics Relevant to Wound Healing

Physicochemical characteristics play a critical role in determining the effectiveness of wound care materials, as they directly influence the interaction between the dressing and the biological environment of the wound[78]. For advanced biomaterials designed for wound healing, properties such as swelling behaviour, moisture retention,

mechanical integrity and degradation kinetics must be carefully balanced to support tissue regeneration while maintaining patient comfort and safety[79]. Fig.3 An optimal wound dressing should be capable of absorbing excess exudate while preserving a moist interface, provide sufficient mechanical support to protect the wound bed and degrade in a controlled manner that aligns with the natural healing process. These interrelated physicochemical features are particularly important for polymer-based nano-hydrogel systems, which are engineered to actively respond to the dynamic conditions present in acute and chronic wounds[80].

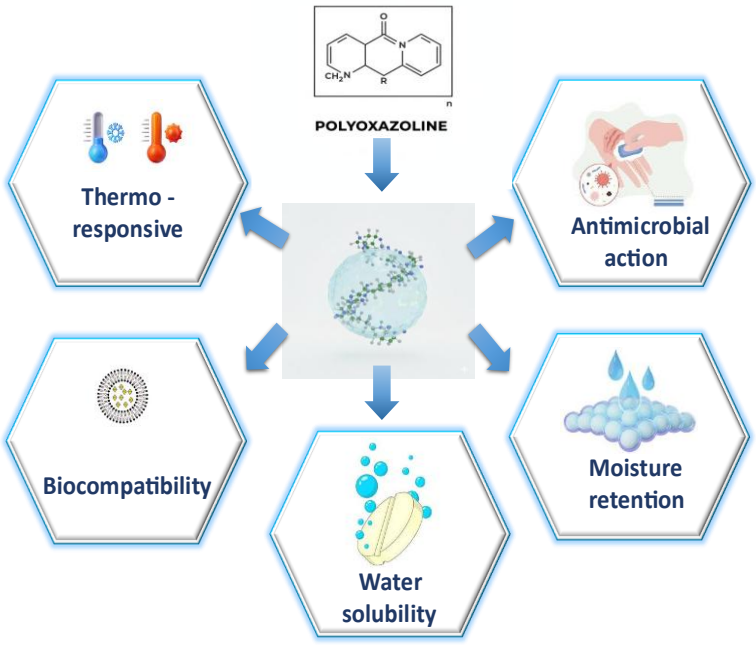


Fig. 3. Physicochemical properties of polyoxazoline relevant to wound healing

5.1. Swelling Behaviour and Moisture Retention

Swelling behaviour and moisture retention are fundamental characteristics influencing the healing outcome[15]. Adequate swelling allows the material to absorb wound exudate, prevent fluid accumulation and reduce the risk of maceration of surrounding tissue[81]. At the same time, excessive swelling can compromise mechanical stability and lead to loss of structural integrity. Therefore, controlled water uptake is essential to maintain an optimal moist environment that supports cell migration, angiogenesis and extracellular matrix formation[82]. Moisture retention also helps regulate local temperature and protects nerve endings, reducing pain and discomfort. In polymer-based wound dressings, swelling behaviour can be tailored by adjusting polymer composition, crosslinking density and network architecture, enabling precise control over hydration levels throughout the healing process[83].

5.2. Mechanical Properties and Structural Stability

Mechanical properties and structural stability are equally important in ensuring effective wound coverage and protection[84]. Wound dressings must be sufficiently robust to withstand handling, application and mechanical stress caused by patient movement, while remaining flexible enough to conform to irregular wound surfaces[85]. Materials that are too rigid may restrict tissue movement and impair cell migration, whereas overly soft structures may collapse or lose integrity under physiological conditions. An ideal dressing exhibits a balance between elasticity and strength, mimicking the mechanical properties of native skin[86]. Structural stability is particularly critical for long-term wound management, as repeated deformation or prolonged exposure to moisture can weaken the material[87]. Properly designed polymer networks maintain their integrity over time, ensuring consistent performance and reducing the need for frequent replacement[88].

5.3. Degradation Kinetics and Biostability

Degradation kinetics and biostability significantly influence the long-term functionality and safety of wound healing materials[89]. Controlled degradation allows the dressing to gradually break down as new tissue forms, minimizing the need for manual removal and reducing the risk of secondary injury[90]. The degradation rate should be synchronized with the healing timeline, ensuring that the material remains intact during critical phases of repair and resorbs once its function is complete. Excessively rapid degradation may lead to premature loss of mechanical support, while slow or incomplete degradation can result in material accumulation and prolonged foreign body presence[91]. Biostability under physiological conditions is also essential to prevent undesirable changes in material properties, such as loss of strength or uncontrolled swelling[92]. Importantly, degradation byproducts should be non-toxic and easily cleared by the body, preserving local tissue compatibility. Together, optimized swelling behaviour, mechanical stability and controlled degradation form the foundation for designing effective wound healing materials capable of supporting regeneration while maintaining safety and comfort[93].

6. Biological Interactions and Healing Mechanisms

Biological interactions between wound healing materials and the surrounding tissue play a decisive role in determining therapeutic success, as healing is governed not only by physical coverage but also by complex cellular and molecular events[94]. Advanced biomaterials designed for wound repair must actively engage with the biological environment to support cell viability, regulate immune responses and promote tissue regeneration[95]. At the wound site, cells are continuously exposed to mechanical cues, biochemical signals and extracellular matrix components that collectively guide healing progression[96]. Materials that harmonize with these processes can accelerate repair, whereas poorly designed systems may provoke inflammation, impair cell function or delay closure. Understanding how biomaterials interact with cells and influence biological pathways is therefore central to the development of effective wound healing strategies[97].

6.1. Cell–Material Interactions

Cell–material interactions are among the earliest and most critical events following material application to a wound[98]. Once a biomaterial comes into contact with biological fluids, proteins rapidly adsorb onto its surface, forming a provisional interface that mediates subsequent cell attachment and behaviour[92]. The surface chemistry, topography and hydration state of the material influence protein conformation and availability of cell-binding sites, which in turn regulate cell adhesion, spreading and migration. Fibroblasts, keratinocytes, endothelial cells and immune cells each respond differently to material cues, highlighting the need for carefully tuned surface properties[79]. Materials that promote fibroblast attachment and proliferation support extracellular matrix synthesis, while those that encourage keratinocyte migration facilitate wound closure. At the nanoscale, increased surface area enhances contact with cells and allows more efficient presentation of biochemical signals[99]. Additionally, compliant and hydrated matrices better mimic native tissue, reducing cellular stress and supporting normal cellular functions. Properly designed materials can thus provide a supportive microenvironment that guides cell behaviour toward regeneration rather than fibrosis or chronic inflammation[100].

6.2. Modulation of Inflammation and Immune Response

The modulation of inflammation and immune response is a key determinant of healing outcomes. Inflammation is an essential early phase of wound repair, enabling debris clearance and defence against infection[101]. However, excessive or prolonged inflammation is a hallmark of chronic wounds and a major barrier to healing. Biomaterials that trigger exaggerated immune responses may activate macrophages and neutrophils excessively, leading to sustained release of proteases and reactive species that damage newly formed tissue[6]. Conversely, materials with immunologically favourable profiles can help restore balance within the wound environment. By minimizing nonspecific immune activation and supporting a shift from pro-inflammatory to pro-healing immune phenotypes, advanced wound materials can facilitate progression to later healing stages[102]. Additionally, localized delivery of anti-inflammatory or immunomodulatory agents from the material matrix allows targeted regulation of immune activity without systemic side effects. Such controlled modulation is particularly valuable in chronic wounds, where dysregulated immune signalling perpetuates tissue damage and delays regeneration[103].

6.3. Angiogenesis, Collagen Deposition and Re-epithelialization

Angiogenesis, collagen deposition and re-epithelialization represent interconnected processes that collectively restore tissue integrity and function[104]. Angiogenesis is essential for supplying oxygen and nutrients to the regenerating tissue and for removing metabolic waste[105]. Impaired vascularization is a common feature of non-healing wounds, leading to hypoxia and reduced cellular activity. Biomaterials that support endothelial cell migration and organization can promote the formation of new capillary networks, improve local perfusion and accelerate repair[106]. This can be achieved through structural features that facilitate cell infiltration as well as through the localized presentation of angiogenic cues. Enhanced vascularization also supports subsequent stages of healing by enabling fibroblasts and keratinocytes to function effectively[107].

Collagen deposition is another critical component of wound healing, as collagen provides structural support and forms the foundation of the newly regenerated tissue[108]. Fibroblasts synthesize and organize collagen fibres, gradually replacing the provisional matrix formed during early healing. Materials that support fibroblast activity and provide appropriate mechanical cues can influence both the quantity and quality of collagen produced[109]. Balanced collagen deposition is essential, as insufficient synthesis weakens the tissue, while excessive or disorganized deposition can lead to fibrosis and scarring. By offering a supportive and hydrated framework, advanced wound materials help regulate matrix formation and promote organized tissue architecture[110].

Re-epithelialization, the final step in surface restoration, involves the migration and proliferation of keratinocytes to cover the wound bed and re-establish the epidermal barrier[111]. Successful re-epithelialization requires a moist environment, minimal inflammation and an intact provisional matrix. Materials that maintain hydration and reduce mechanical disruption support keratinocyte movement and attachment[112]. Additionally, reducing bacterial burden and inflammatory stress further enhances epithelial regeneration. When these conditions are met, epithelial cells can effectively close the wound and restore barrier function, reducing the risk of infection and recurrence[113].

7. Therapeutic Loading and Controlled Drug Delivery

Therapeutic loading and controlled drug delivery are central features of advanced wound care systems, as effective healing often requires the localized and sustained presence of multiple therapeutic agents[114]. Wounds, particularly chronic and infected ones, exhibit complex pathological environments characterized by microbial colonization, persistent inflammation, oxidative stress and impaired cellular signalling. Conventional topical

treatments frequently fail to maintain therapeutic concentrations at the wound site due to rapid diffusion, degradation or repeated removal during dressing changes[115]. Controlled delivery platforms are therefore designed to overcome these challenges by protecting sensitive therapeutics, regulating their release and ensuring prolonged bioactivity directly within the wound microenvironment[12]. By integrating drug delivery functions into wound dressings, it becomes possible to address infection, inflammation and tissue regeneration simultaneously while minimizing systemic exposure and associated side effects[116].

7.1. Encapsulation of Antimicrobial and Anti-Inflammatory Agents

Encapsulation of antimicrobial and anti-inflammatory agents is a critical strategy for managing wound-associated complications[117]. Microbial infection remains one of the leading causes of delayed wound healing, as bacterial colonization triggers prolonged inflammation and tissue damage[118]. Encapsulation within polymeric matrices protects antimicrobial agents from premature degradation and enables their gradual release at effective local concentrations. Sustained antimicrobial delivery helps suppress bacterial growth over extended periods, reducing the need for frequent reapplication and lowering the risk of antibiotic resistance associated with subtherapeutic dosing[119]. In parallel, anti-inflammatory agents play a vital role in regulating excessive immune responses that hinder healing. Encapsulation allows these agents to be released in a controlled manner, maintaining inflammation at levels conducive to tissue repair without completely suppressing essential immune functions. Localized delivery also reduces the likelihood of systemic adverse effects, which is particularly important for long-term treatment of chronic wounds[120].

7.2. Growth Factor and Bioactive Molecule Delivery

The delivery of growth factors and other bioactive molecules is essential for restoring impaired regenerative signalling pathways[121]. Growth factors regulate key cellular processes such as proliferation, migration, angiogenesis and extracellular matrix synthesis. In chronic wounds, the activity of endogenous growth factors is often diminished due to enzymatic degradation or reduced expression[122]. Direct topical application of these molecules is typically ineffective, as they are rapidly degraded or diffused away from the wound site. Encapsulation within delivery systems provides a protective environment that preserves bioactivity and enables sustained release over clinically relevant timeframes[123]. This localized and prolonged exposure enhances cellular responsiveness and promotes coordinated tissue regeneration. In addition to growth factors, other bioactive molecules such as antioxidants, peptides and cytokine modulators can be incorporated to address oxidative stress and signalling imbalances commonly observed in non-healing wounds[124]. The ability to co-deliver multiple therapeutic agents further enhances treatment efficacy by targeting different stages of the healing process simultaneously[125].

7.3. Stimuli-Responsive Release Strategies

Stimuli-responsive release strategies represent a sophisticated approach to controlled drug delivery in wound care, enabling materials to respond dynamically to changes in the wound environment[126]. Wounds exhibit distinct physiological cues, including variations in pH, temperature, enzymatic activity and reactive species levels, which can be exploited to trigger on-demand drug release. For instance, materials designed to respond to acidic pH can selectively release antimicrobial agents in infected wounds, where pH is often lowered to bacterial metabolism[127]. Enzyme-responsive systems can degrade or alter their structure in the presence of wound-specific enzymes, enabling targeted release at sites of active tissue remodelling[117]. Similarly, redox-responsive systems can respond to elevated oxidative stress by releasing antioxidants or anti-inflammatory agents. These adaptive delivery mechanisms ensure that therapeutics are released when and where they are most needed, enhancing efficacy while minimizing unnecessary exposure[128].

The integration of controlled and stimuli-responsive drug delivery into wound care materials also improves patient compliance and overall treatment outcomes[126]. By reducing the frequency of dressing changes and maintaining consistent therapeutic levels, such systems minimize wound disturbance and promote uninterrupted healing[129]. Additionally, controlled release reduces peak drug concentrations that could cause cytotoxic effects, ensuring a safer therapeutic profile. Importantly, the tunability of these delivery systems allows customization based on wound type, severity and patient-specific factors, supporting a more personalized approach to wound management[130].

8. Applications in Wound Healing

Advanced wound care materials have found broad application across diverse wound types, reflecting their ability to address the distinct biological and clinical challenges associated with different injury conditions[87]. Effective wound management requires tailored strategies that consider wound depth, duration, vascularization, infection risk and patient-specific factors[131]. Modern biomaterial-based systems are increasingly designed to provide both protective and therapeutic functions, enabling improved healing outcomes in acute injuries as well as complex, non-healing wounds. Their versatility allows adaptation to various clinical scenarios, ranging from short-term surgical wounds to long-standing ulcers and severe tissue damage caused by burns or ischemia[132].

8.1. Acute Wounds and Surgical Injuries

In acute wounds and surgical injuries, the primary goals are rapid closure, infection prevention and minimal scarring[133]. These wounds typically progress through the normal stages of healing; however, surgical interventions and traumatic injuries can still be complicated by inflammation, contamination or mechanical stress[134]. Advanced wound care materials support acute wound healing by maintaining a moist environment that facilitates cell migration and epithelial regeneration while protecting the wound from external pathogens[135].

Their ability to conform closely to the wound surface reduces dead space and promotes uniform healing. Additionally, localized delivery of antimicrobial or anti-inflammatory agents helps prevent post-operative infections and excessive inflammatory responses, thereby accelerating recovery and improving cosmetic outcomes[136]. Reduced dressing changes further minimize tissue disturbance and patient discomfort during the healing period[137].

8.2. Chronic Wounds and Diabetic Ulcers

Chronic wounds, including diabetic foot ulcers, venous leg ulcers and pressure injuries, present far greater clinical challenges due to impaired vascularization, prolonged inflammation and reduced cellular responsiveness[138]. These wounds often fail to heal despite standard care, leading to recurrent infections, tissue necrosis and, in severe cases, amputation. Advanced wound care systems offer distinct advantages in managing chronic wounds by addressing multiple pathological factors simultaneously[139]. Sustained moisture regulation prevents desiccation while controlling excess exudate, creating conditions favourable for tissue regeneration. Controlled release of therapeutic agents supports infection control, modulates inflammation and stimulates angiogenesis and fibroblast activity[140]. In diabetic ulcers, where oxidative stress and poor blood flow are common, targeted delivery of antioxidants and regenerative cues can help restore balance within the wound microenvironment. The adaptability of these systems enables prolonged treatment without frequent intervention, which is particularly beneficial for patients with limited mobility or compromised immune function[141].

8.3. Burns and Ischemic Wounds

Burns and ischemic wounds represent some of the most severe forms of tissue injury, often involving extensive tissue loss, high infection risk and impaired perfusion[142]. In burn wounds, rapid fluid loss, inflammation and microbial invasion pose immediate threats to patient survival and long-term recovery[143]. Advanced wound materials provide effective coverage by retaining moisture, absorbing exudate and forming a protective barrier against infection. Their soft and hydrated nature supports pain reduction and prevents adherence to newly formed tissue, reducing trauma during dressing changes[47]. For ischemic wounds, where oxygen and nutrient supply are compromised, materials that promote angiogenesis and support cellular metabolism are particularly valuable. By enhancing local vascularization and maintaining a favourable healing environment, these systems contribute to improved tissue viability and wound closure[107]. Across acute, chronic and complex wounds, advanced wound care technologies continue to expand therapeutic possibilities, offering more effective, patient-friendly solutions for diverse wound healing applications[144].

9. Challenges and Translational Barriers

Despite significant advances in wound care technologies, several challenges and translational barriers continue to limit the successful transition of innovative materials from laboratory research to routine clinical practice[145]. While many advanced systems demonstrate promising performance in controlled experimental settings, their large-scale production, long-term safety and clinical validation remain complex and resource-intensive. Addressing these barriers is essential to ensure that new wound healing technologies are not only scientifically effective but also manufacturable, safe and compatible with regulatory and clinical requirements[146]. The gap between bench-scale innovation and bedside application highlights the need for integrated strategies that align material design with practical deployment considerations[117].

9.1. Manufacturing and Scalability Issues

Manufacturing and scalability represent major obstacles in the translation of advanced wound care materials[87]. Many fabrication techniques optimized at the laboratory level rely on precise control over polymer composition, particle size or network architecture, which can be difficult to reproduce consistently at industrial scale[147]. Batch-to-batch variability, sensitivity to processing conditions and reliance on specialized equipment can compromise product uniformity and increase production costs. Scaling up synthesis while maintaining quality, sterility and performance requires robust manufacturing protocols and stringent quality control measures[148]. Additionally, the use of complex or multi-step fabrication processes may hinder cost-effective production, limiting accessibility in resource-constrained healthcare settings. Developing scalable, reproducible and economically viable manufacturing methods remains a critical challenge for widespread clinical adoption[149].

9.2. Safety, Toxicity and Regulatory Considerations

Safety, toxicity and regulatory considerations are equally important barriers that must be carefully addressed before clinical translation[150]. Wound healing materials are often applied directly to damaged tissue, where barrier function is compromised, increasing the risk of local or systemic adverse effects[116]. Comprehensive evaluation of cytotoxicity, immunogenicity and long-term biocompatibility is therefore essential. Degradation products and residual reagents used during fabrication must be assessed for potential toxicity and accumulation in the body[151]. Furthermore, differences in regulatory frameworks across regions can complicate approval pathways, particularly for products that combine device and drug functions. Navigating these regulatory landscapes requires early consideration of compliance standards and alignment of material design with regulatory expectations[152].

9.3. Clinical Evaluation and Standardization

Clinical evaluation and standardization present additional hurdles in translating advanced wound care technologies[87]. Wounds vary widely in etiology, severity and patient-specific factors, making it challenging to design clinical studies that accurately reflect real-world conditions[153]. Variability in wound assessment methods, outcome measures and treatment protocols can hinder comparison across studies and slow regulatory

approval. Standardized criteria for evaluating healing progression, infection control and patient-reported outcomes are needed to ensure consistent and meaningful clinical data[154]. Additionally, long-term clinical studies are often required to assess durability, recurrence rates and potential delayed adverse effects, further increasing development timelines. Limited access to large patient populations and high trial costs can also restrict comprehensive clinical evaluation[155]. Overcoming these challenges will require collaboration between researchers, clinicians, manufacturers and regulatory bodies to establish harmonized standards, streamlined evaluation pathways and translational frameworks that support the successful integration of innovative wound care solutions into clinical practice[156].

10. Future Perspectives and Emerging Trends

The future of wound care is increasingly shaped by the convergence of material science, bioengineering and digital health, driving the development of next-generation therapeutic platforms that move beyond passive wound coverage[12]. Emerging research focuses on smart and multifunctional nano-hydrogel systems capable of actively sensing, responding to and modulating the wound microenvironment in real time[80]. These advanced materials are designed to address the complex and evolving nature of wounds, particularly chronic and non-healing conditions, where conventional treatments often fail. By integrating multiple therapeutic functions into a single platform, future nano-hydrogel systems aim to provide personalized, adaptive and more effective wound management strategies[157].

Smart nano-hydrogel systems are being engineered with built-in responsiveness to specific physiological cues present in wounds, such as changes in pH, temperature, enzymatic activity or oxidative stress levels[158]. These stimuli-responsive properties enable materials to release therapeutic agents in a controlled and on-demand manner, ensuring that treatment is delivered precisely when and where it is needed. For example, a hydrogel that responds to acidic conditions may selectively release antimicrobial agents in infected wounds, while remaining inactive in healthy tissue[159]. Similarly, enzyme-responsive systems can adapt to elevated protease levels in chronic wounds, adjusting their degradation or drug release profiles accordingly[160]. This level of responsiveness reduces unnecessary drug exposure, minimizes side effects and improves overall therapeutic efficiency. In addition to drug delivery, smart hydrogels can be designed to alter their mechanical properties or swelling behaviour in response to wound conditions, maintaining optimal hydration and structural support throughout the healing process[43].

By incorporating antimicrobial, anti-inflammatory and pro-regenerative agents within the same platform, multifunctional hydrogels can coordinate multiple healing pathways[14]. This integrated approach is particularly valuable for chronic wounds, where prolonged inflammation, microbial colonization and impaired cellular activity coexist[161]. Furthermore, advances in polymer chemistry allow precise spatial and temporal control over therapeutic release, enabling sequential delivery of agents aligned with different stages of healing. Such staged treatment strategies have the potential to more closely mimic natural healing processes and reduce the risk of treatment failure[129].

The integration of smart nano-hydrogel systems with advanced wound care technologies represents a major trend in the evolution of wound management[46]. One promising direction involves combining hydrogels with biosensing technologies capable of monitoring wound conditions in real time[162]. Embedded sensors can detect changes in parameters such as pH, temperature, oxygen levels or bacterial metabolites, providing valuable information about wound status and healing progression[163]. When coupled with responsive hydrogels, this data can trigger automated therapeutic responses, creating closed-loop treatment systems. These intelligent dressings have the potential to reduce the need for frequent clinical assessments, enable early detection of complications and support timely intervention[164].

Another emerging trend is the integration of nano-hydrogels with advanced delivery and fabrication technologies[165]. Techniques such as additive manufacturing and bio-fabrication enable the creation of customized wound dressings tailored to patient-specific wound geometry and healing requirements[166]. Personalized hydrogel constructs can be designed to match wound size, depth and shape, improving coverage and therapeutic efficacy[167]. Additionally, combining hydrogels with micro- or nano-scale delivery devices allows more precise control over therapeutic dosing and distribution. Such hybrid systems expand the functional capabilities of wound dressings and support more targeted and efficient treatment strategies[168].

Digital health and data-driven approaches are also expected to play an increasingly important role in future wound care. The integration of smart hydrogels with wireless communication technologies enables remote monitoring of wound conditions and treatment performance[169]. Clinicians can access real-time data to assess healing progress, adjust treatment protocols and intervene promptly when complications arise. This approach not only improves clinical decision-making but also enhances patient engagement and adherence to treatment[170]. For patients with chronic wounds, remote monitoring reduces the need for frequent clinic visits, improving quality of life and reducing healthcare costs[171]. Looking ahead, the successful translation of smart and multifunctional nano-hydrogel systems will depend on addressing challenges related to scalability, regulatory approval and clinical validation[172]. Interdisciplinary collaboration among material scientists, engineers, clinicians and regulatory experts will be essential to ensure that emerging technologies meet both scientific and practical requirements[173]. As these challenges are progressively overcome, the integration of intelligent materials with advanced wound care technologies is expected to transform wound management, offering more responsive, personalized and effective therapeutic solutions that align with the evolving demands of modern healthcare[87].

11. CONCLUSION

Polyoxazoline-based nano-hydrogels represent a promising advancement in wound care by uniting precise polymer chemistry with biologically responsive material design. Throughout this work, their relevance has been highlighted across key aspects of wound management, including moisture regulation, mechanical support, controlled degradation and active biological interaction. The ability of these systems to modulate inflammation, prevent infection and promote angiogenesis, collagen deposition and re-epithelialization positions them as effective alternatives to conventional dressings. Moreover, their capacity for therapeutic loading and stimuli-responsive drug release enables localized, sustained treatment tailored to the evolving wound microenvironment. Despite existing challenges related to manufacturing scale-up, safety assessment and clinical standardization, ongoing advances in polymer synthesis, nanofabrication and regulatory frameworks continue to narrow the translational gap. With further interdisciplinary collaboration and robust clinical validation, polyoxazoline-based nano-hydrogels hold significant potential to transform wound healing strategies, offering smarter, multifunctional and patient-centred solutions for both acute and chronic wounds.

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