INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Formulation and Evaluation of Self-Healing Chitosan–Pectin Hydrogel Loaded with Centella asiatica Extract for Chronic Wound Healing: A Review

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ARTICLE INFO

Published: 17 Jun. 2026
Keywords:
Chronic wounds, diabetic ulcers, Centella asiatica, polysaccharide, antimicrobial properties.
DOI:
10.5281/zenodo.20728000

ABSTRACT

Chronic wounds, including diabetic ulcers, pressure sores, and venous ulcers, represent a significant clinical challenge due to their stalled inflammatory phase and susceptibility to mechanical failure of dressing materials. Self-healing hydrogels have emerged as a revolutionary class of biomaterials capable of autonomous structural repair, thereby extending the functional lifespan of wound dressings. This review explores the synergistic potential of chitosan and pectin—two abundant, biocompatible natural polymers—in forming a dynamic cross-linked network. Furthermore, the integration of Centella asiatica extract, rich in triterpenoids like asiaticoside, provides potent bioactive cues for collagen synthesis and re-epithelialization. This paper evaluates the chemical mechanisms underlying self-healing properties, the pharmacological role of Centella asiatica, and the analytical techniques required to validate the efficacy of these hydrogels in chronic wound management.

INTRODUCTION

Chronic wounds are characterized by a failure to proceed through the orderly and timely sequences of repair, typically remaining stalled in the inflammatory phase for more than three months [1]. The global prevalence of chronic wounds is rising, driven by an aging population and the epidemic of diabetes mellitus. Traditional dressings often fail to provide the necessary moist environment or succumb to mechanical stresses caused by patient movement, leading to premature degradation and loss of barrier function.

Recent advancements in polymer science have introduced "smart" biomaterials, specifically self-healing hydrogels. These materials can spontaneously repair internal or external damage, restoring their structural integrity without external intervention [2]. Among the polymers used, Chitosan (CS) and Pectin (PEC) are particularly attractive due to their opposing charges and

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

biocompatibility. Chitosan, a cationic polysaccharide derived from chitin, possesses inherent antimicrobial properties, while Pectin, an anionic heteropolysaccharide, offers excellent gelling and pH-responsive characteristics [3].

The therapeutic efficacy of these hydrogels can be significantly enhanced by the incorporation of phytopharmaceuticals. *Centella asiatica* (L.) Urb., commonly known as Gotu Kola, has been used for centuries in traditional medicine for skin repair. Its primary active constituents, including asiaticoside, madecassoside, and their respective acids, are known to stimulate fibroblast proliferation and type I collagen synthesis [4]. This review focuses on the formulation strategies, cross-linking mechanisms, and evaluative parameters of a self-healing CS-PEC hydrogel system loaded with *Centella asiatica* for chronic wound applications.

II. Pathophysiology of Chronic Wounds and the Need for Bioactive Dressings

Chronic wounds differ from acute wounds due to a persistent pro-inflammatory environment characterized by high levels of matrix metalloproteinases (MMPs), pro-inflammatory cytokines (IL-1β, TNF-α), and excessive reactive oxygen species (ROS) [5]. This environment degrades the extracellular matrix (ECM) and inactivates growth factors, preventing the transition to the proliferative phase.

An ideal dressing for such wounds must:

1. Maintain a moist environment to facilitate autolytic debridement.
2. Provide a barrier against microbial invasion.
3. Possess mechanical durability yet remain flexible.
4. Actively deliver bioactive agents to modulate the healing process [6].

Self-healing hydrogels address the mechanical durability aspect. In chronic wounds located over joints or areas of high mobility, standard hydrogels often crack. A self-healing matrix can reconnect its polymer chains through dynamic bonding, ensuring continuous protection and sustained drug release [7].

III. Polymer Matrix: Chitosan and Pectin Synergy

A. Chitosan (CS)

Chitosan is a linear polysaccharide composed of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine. Its primary amine groups become protonated in acidic media, making it the only natural cationic polymer [8]. This allows for the formation of polyelectrolyte complexes (PEC) with anionic polymers. Chitosan promotes hemostasis and exhibits mucoadhesive properties, which are critical for prolonged contact with the wound bed [9].

B. Pectin (PEC)

Pectin is a complex structural polysaccharide found in plant cell walls, primarily consisting of α-(1→4)-linked D-galacturonic acid. Depending on the degree of esterification (DE), pectin can form gels under different conditions. In wound healing, pectin serves as a moisture-retentive agent and provides a localized acidic pH that can inhibit certain bacterial strains [10].

C. Polyelectrolyte Complexation and Dynamic Bonding

The combination of CS and PEC results in a Polyelectrolyte Complex (PEC) through electrostatic interactions between the groups of chitosan and the groups of pectin [11]. However, to achieve true "self-healing" properties, dynamic covalent bonds or strong physical interactions (like

hydrogen bonding or hydrophobic associations) must be engineered into the matrix.

IV. Mechanisms of Self-Healing in Hydrogels

Self-healing in hydrogels is generally categorized into physical and chemical mechanisms.

A. Dynamic Covalent Bonding (Schiff Base Reaction)

The most common strategy for CS-based self-healing hydrogels involves the Schiff base reaction. By oxidizing pectin (using sodium periodate) to form dialdehyde pectin (DAP), the aldehyde groups can react with the primary amine groups of chitosan to form reversible imine bonds [12]. These bonds can break and reform dynamically in response to mechanical stress or pH changes, allowing the hydrogel to "heal" at the cleavage site.

B. Hydrogen Bonding and Ionic Interactions

Chitosan and pectin contain numerous hydroxyl and carboxyl groups that participate in extensive hydrogen bonding. While individually weak, the collective strength of these bonds contributes to the visco-elastic recovery of the material [13]. Furthermore, the reversible nature of ionic cross-linking between CS and PEC allows the network to re-establish its structure after deformation.

V. *Centella asiatica*: The Bioactive Cargo

Centella asiatica (CA) is a medicinal herb belonging to the Apiaceae family. Its wound-healing properties are attributed to its pentacyclic triterpenes.

A. Active Phytoconstituents

1. **Asiaticoside:** Enhances the induction of antioxidant enzymes and increases hydroxyproline content, which is a marker for collagen deposition [14].
1. **Madecassoside:** Specifically targets the TGF-β/Smad signaling pathway, promoting the migration of fibroblasts and reducing inflammation [15].
2. **Asiatic and Madecassic Acids:** These aglycones stimulate the synthesis of glycosaminoglycans (GAGs) and improve the tensile strength of the newly formed tissue.

B. Mechanism of Action in Chronic Wounds

In chronic wounds, CA extract acts by:

1. **Reducing Oxidative Stress:** Scavenging ROS that contribute to tissue damage.
2. **Anti-inflammatory Effects:** Downregulating NF-κB signaling to reduce cytokine production [16].
3. **Angiogenesis:** Promoting the formation of new blood vessels (neovascularization) to restore oxygen and nutrient supply to the necrotic wound bed [17].

VI. Formulation Strategies

The development of a CA-loaded CS-PEC self-healing hydrogel involves several critical steps:

1. **Preparation of Dialdehyde Pectin (DAP):** Pectin is subjected to periodate oxidation to introduce aldehyde groups required for the Schiff base reaction [18].
2. **Preparation of Chitosan Solution:** CS is typically dissolved in 1-2% acetic acid.
3. **Incorporation of *Centella asiatica*:** The extract (standardized for asiaticoside content) is dispersed within the polymer solution. Care must be taken to ensure the solubility of the extract, possibly using a co-solvent or surfactant if necessary.

4. **Gelation:** Mixing the DAP and CS solutions under controlled stirring. The ratio of CS to PEC is pivotal in determining the pore size, swelling ratio, and self-healing efficiency [19].

VII. Evaluation and Characterization

To ensure the clinical viability of the hydrogel, rigorous evaluation is required.

A. Physico-chemical Characterization

1. **Fourier Transform Infrared Spectroscopy (FTIR):** To confirm the formation of Schiff base (imine) bonds (typically observed around 1640-1660 cm^-1 and the successful incorporation of CA extract [20].
2. **Scanning Electron Microscopy (SEM):** To analyze the surface morphology and porosity. A highly porous structure (pore size 100-200 μm) is essential for gas exchange and nutrient transport [21].
3. **Swelling and Degradation:** Chronic wounds often produce high amounts of exudate. The hydrogel must be able to absorb significant amounts of fluid without losing structural integrity.

B. Self-Healing Efficiency

1. **Macroscopic Observation:** Cutting the hydrogel into two pieces and placing them in contact to observe autonomous fusion over time.
2. **Rheological Analysis:** Step-strain tests are used to measure the recovery of storage modulus and loss modulus after high-strain deformation. A rapid recovery indicates efficient self-healing [22].

C. *In Vitro* Release Studies

The release profile of asiaticoside from the CS-PEC matrix is usually studied using a Franz diffusion cell. A biphasic release—initial burst release to reach therapeutic levels followed by sustained release—is ideal for chronic wound management [23].

D. Biological Evaluation

1. **Cytotoxicity (MTT Assay):** Testing against human dermal fibroblasts (HDF) or keratinocytes (HaCaT) to ensure the material is non-toxic [24].
2. ***In Vitro* Scratch Assay:** Measuring the rate of "wound" closure in a cell monolayer to quantify the migratory stimulus provided by the CA-loaded hydrogel [25].
3. **Antibacterial Activity:** Assessing the zone of inhibition against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, common pathogens in chronic ulcers.

VIII. *In Vivo* Efficacy and Clinical Translation

Animal models, particularly streptozotocin-induced diabetic rats, are frequently used to simulate chronic wound conditions. Studies have shown that hydrogels containing CS and CA significantly accelerate wound contraction compared to commercial dressings. Histological analysis typically reveals increased collagen density, better-organized granulation tissue, and reduced inflammatory cell infiltration in the CA-CS-PEC treated groups [26].

However, translating these results to human clinical trials requires addressing challenges such as the standardization of CA extracts, the long-term stability of the Schiff base bonds in varying wound pH, and the cost-effectiveness of the manufacturing process [27].

IX. Discussion: Synergy and Future Directions

The synergy between the self-healing CS-PEC matrix and *Centella asiatica* creates a "bioactive-

instructive" environment. While the polymers provide the mechanical and physical scaffold, the CA extract provides the chemical signals necessary to restart the healing clock. The self-healing property is not merely a mechanical advantage; it ensures that the drug delivery system remains intact, preventing "dose dumping" if the dressing were to fail under stress [28].

Future research should focus on:

1. **Multi-stimuli Responsiveness:** Engineering hydrogels that respond to wound pH or temperature to trigger the release of CA only when needed.
2. **3D Bioprinting:** Using CS-PEC as a bio-ink to create patient-specific wound dressings that match the geometry of complex ulcers [29].
3. **Combination Therapy:** Incorporating other agents, such as silver nanoparticles or growth factors, alongside CA to address multi-drug resistant infections.

CONCLUSION

The development of a self-healing hydrogel based on Chitosan and Pectin loaded with *Centella asiatica* represents a sophisticated approach to chronic wound care. By combining the regenerative power of traditional herbal medicine with the structural innovation of dynamic covalent chemistry, this system addresses both the mechanical and biological deficiencies of current treatments. The reversible nature of the CS-PEC network provides durability, while the sustained release of triterpenoids promotes essential cellular processes. Although further clinical validation is required, this composite hydrogel stands as a promising candidate for improving the quality of life for patients suffering from non-healing wounds.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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HOW TO CITE: Naimish Bajpai, Ayush Bajpai,Nidhi Srivastava, Formulation and Evaluation of Self-Healing Chitosan–Pectin Hydrogel Loaded with Centella asiatica Extract for Chronic Wound Healing: A Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 4084-4090. https://doi.org/ 10.5281/zenodo.20728000