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RESEARCH ARTICLE

Nanoparticle-Loaded Alginate for Advanced Wound Care: A Review on Innovations and Challenges

D Neha[1], R Anusha[2], Halima Nachiyar[3] and V Ramnath[4*]
[1]Meenakshi Academy of Higher Education and Research (MAHER), ChennaiAcharya Institute of Allied Health Science, Bangalore,
[2]Meenakshi Ammal Dental College and Hospital, Maduravoil, Chennai.
[3]Meenakshi Academy of Higher Education and Research (MAHER), Chennai Department of Laboratory Medicine and Pathology, Dubai Health, Dubai, UAE.

*Corresponding Author
V Ramnath4

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Abstract: Wound healing is a complex and dynamic process which involving the inflammation, proliferation and tissue re-modeling often hindered in chronic conditions such as diabetic ulcers pressure sores, and burns. Alginate a naturally derived polysaccharides from brown seaweeds, has gained significant attention in wound management due to its biocompatibility, biodegradability, moisture retention and gel – forming ability. Recent advancements in nanotechnology have expanded the therapeutic potential of alginate by incorporating nanoparticles (NPs) with antimicrobial, anti – inflammatory, angiogenic and regenerative properties. Metallic nanoparticles (silver, gold, zinc oxide, copper oxide), polymeric nanoparticles (chitosan, PLGA), lipid – based nanoparticles (liposomes, SLNs), and carbon – based nanomaterials (graphene oxide, CNTs) have demonstrated synergistic effects when integrated with alginate matrices, enhancing wound healing through infection control, modulation of oxidative stress, promotion of vascularization, and controlled drug delivery. Fabrication techniques such as electrospinning, freeze – drying, bioprinting, and cross – linking have enabled the development of innovative alginate – NP dressings tailored for clinical use. Despite these advancements, challenges remain in nanoparticles stability, cytotoxicity, large – scale production, and regulatory approval. This review highlights recent innovations, mechanism of action, clinical application, and future perspectives of nanoparticles – loaded alginate systems, emphasizing their potential as next generation wound dressings for personalized and regenerative medicine.

Keywords – Alginate, Nanoparticles, Wound healing, nanoparticles, Drug delivery, Biocompatibility, Advanced wound dressing, Regenerative medicine.

INTRODUCTION

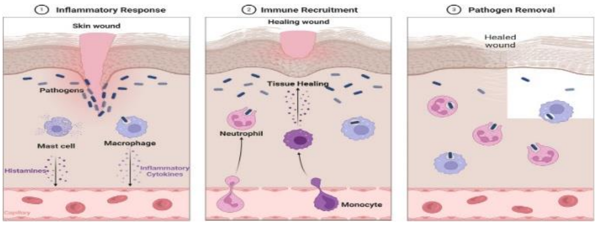


Figure 1 – Wound healing[3]

Skin is the largest organ in human body and play crucial role in different processes such as hydration, protection from chemicals and pathogens, vitamin D synthesis initialization, excretion and thermal regulation[1]. The epidermis or outer layer made up of mostly dead cells with a protein called Keratin which makes the layer waterproof and responsible for protection against the environment. The dermis or middle layer made up of living cells and have blood vessels and nerve that run through and primarily responsible for insulation and shock absorbency. Cells on the surface of the skin are constantly being replaced by regenerative from below with the top layers sloughing off. Science of wound healing is recorded as "three healing gestures" and describes as Washing the wound, making plasters and bandaging the wound. Wounds are generally classified as wounds without tissue loss e.g. in surgery and wounds with tissue loss, such as burn wounds, wounds caused as a result of trauma, abrasions or as secondary events in chronic ailments E.g.- Venous stasis, diabetic ulcers or pressure sores and iatrogenic wound such as skin graft donor sites and dermabrasions. Wounds are classified by the layers involved, superficial wounds involve only the epidermis and dermis, and full thickness wounds involve the subcutaneous fat or deeper tissue[2]. Wound- healing is the process in which Wound healing is divided into three phases – the inflammatory phase, the proliferative phase, and the remodeling phase **figure 1**. The inflammatory phase- which includes the haemostatic phase, the proliferative phase and the regenerative phase. Immunomodulatory responses which play a pivotal role throughout the entire wound healing process which crucially regulating the inflammatory response, facilitating repair and controlling scar formation[3]. The platelet – derived growth factor and other factors which promote the collagen degradation and the transformation of fibroblasts and the growth of new vessels and re – epithelization. All these processes occur at the same time but in a synchronized fashion. Mediators like serotonin and histamine are released from platelet and increase cellular permeability. Platelet derived growth factor attracts the fibroblasts and along with the transforming growth factor which enhances the division and multiplication of fibroblasts, and the fibroblasts in turn into synthesize the collagen. Proliferative or granulation phase does not occur at a distance time but ongoing all the time in the background. Day 12 to 24 months which involves the fibroblasts have starts to lay down new collagen and glycosaminoglycans[4].

Nanotechnology in Wound Healing

- Introduction to nanoparticles (NPs) and their advantages.
- How NPs improve wound healing (antimicrobial, anti-inflammatory, regenerative).
- Need for incorporating NPs into alginate-based systems.

Biosynthesis of Nanoparticles are using natural plant extract with biomedical potentialities like antimicrobial and anti- cancerous etc and it is cost- effective, user friendly, and mostly mild in reaction with no or minimal use of hazardous chemicals[7].

Role of Alginate in Wound Healing

- Natural polysaccharide derived from brown seaweed.
- Hydrophilic nature, exudate absorption, and biocompatibility.
- Clinical significance in wound healing.

Alginate is a water-soluble natural polysaccharide, consisting of salts of alginic acid and mostly obtained from brown seaweed[7,9]. Alginate is a biomedical that found for numerous applications in biomedical science and engineering due to the favourable properties and including biocompatibility and ease of gelation. Alginate has been extensively investigated and used for many biomedical applications and due to its biocompatibility, low toxicity, relatively low cost, and mild gelation by addition of divalent cations such as $Ca2^{+}$. Alginate hydrogels work in wound healing, drug delivery, and tissue engineering application to date. Alginate wound dressing maintain a physiologically moist microenvironment, minimize bacterial infection at the wound site and facilitate wound healing[4].Alginate use as inactive in drug delivery because of its low toxicity, low immunogenicity and biocompatibility the reason is the presence of carboxylic acid groups becomes non – ionized and its pH responsive characteristics and alginate can be used for controlled oral medication administration. Alginic acid can be recovered from marine algae by solubilizing in a dilute alkaline solution and then treating it with mineral acids before it is transformed into salts[9].

Properties of Alginate for Wound Healing

Alginates are salts of long – chain alginic acids, that brown seaweeds are present mainly as the calcium salt of alginic acid, magnesium, potassium and sodium salts are present. Among them the sodium alginates are water soluble polymers, which give highly viscous solutions. The presence of polyvalent cations, such as calcium, sodium alginate has the ability to form gel[5].

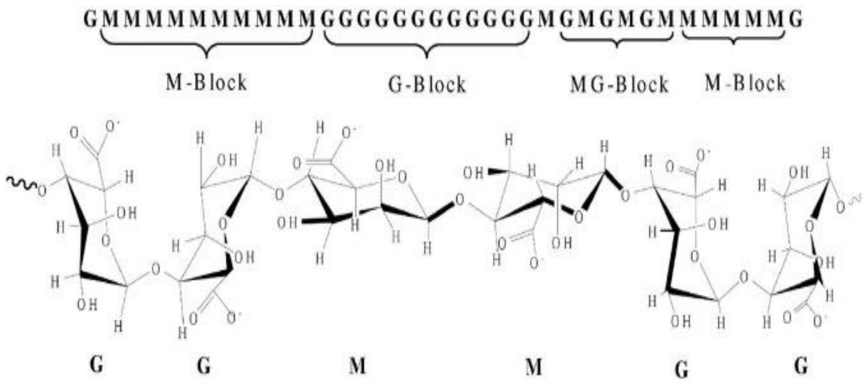


Figure 4 – Alignate chain sequence and the macromolecular confomation[5]

Biological Properties

- Biodegradability and non-toxicity.
- Gel-forming ability and moisture retention.
- Role in cell proliferation and migration.

Alginates also characterised by unique biological and pharmacological properties. Application of biomedical fields but in a sector of wound management material based on alginates and their influence on wound healing[5].

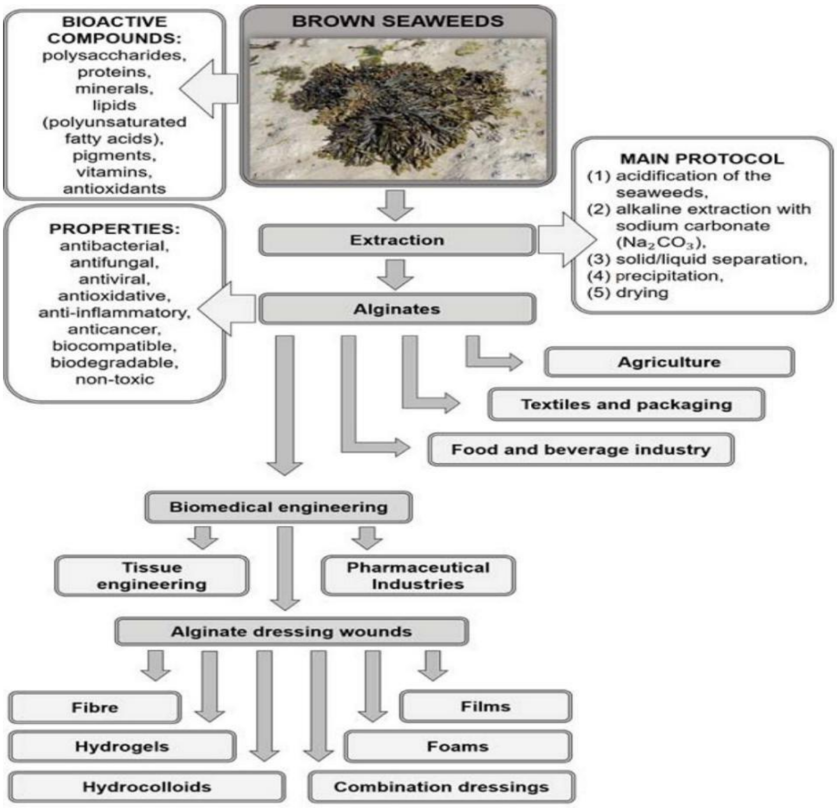


Figure 5: Alginates processing scheme with potential application[5]

Physicochemical Properties

- Ionic cross-linking behavior.
- Water-holding capacity and exudate absorption.
- Interaction with other biomaterials for enhanced wound care.

It is important aspect because mechanical and physiochemical properties which determines the alginates application[5].

TYPES OF NANOPARTICLES INCORPORATED INTO ALGINATE FOR WOUND HEALING

METALLIC NANOPARTICLES

Silver Nanoparticles (AgNPs)

- Strong antimicrobial and anti-biofilm activity.
- Mechanism: disruption of bacterial membranes, reactive oxygen species (ROS) generation.

Polymeric hydrogels containing silver nanoparticles (AgNPs) have attracted great attention for set of applications in the biomedical field and contributed to the antimicrobial and healing properties of silver[6]. Over the fast few years AgNPs collect extremely large interest in biomedical research and remarkable applications in antibacterial, anti – cancer and wound healing therapies. Antibacterial and anti – cancer properties where AgNPs plays a crucial role in wound healing and antimicrobial properties which create a favourable environment for tissue regeneration and wound closure and making the valuable components in advanced in wound care materials. In the field of anticancer research AgNPs exhibited promising capabilities in targeting and inhibiting tumor growth[11].

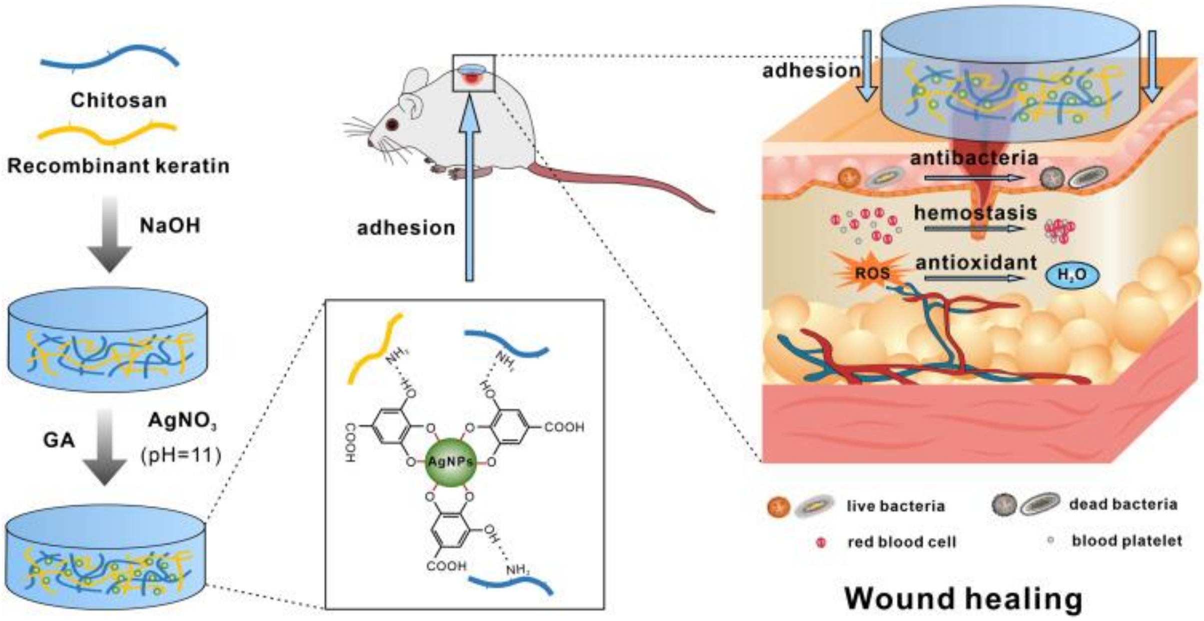


Fig 6: Wound Healing[12]

Gold Nanoparticles (AuNPs)

- Anti-inflammatory and pro-angiogenic effects.
- Potential in accelerating skin regeneration.

Gold nanoparticles have broad application prospects in cancer diagnosis and treatment because of their unique optical and Surface Plasmon Resonance (SPR) properties. Synthesis method of gold nanoparticles is simple and it consists of three main methods: physical, chemical and biological processes. The characteristics of biocompatibility, non – toxicity and no side effects contributed to the anti – cancer therapy. Gold nanoparticles can be used in photothermal therapy, photodynamic therapy and photoimaging which based on their favourable conductivity for heat. Photothermal therapy where nanoparticles encapsulated within tumours produce the thermal energy when exposed to exogenously administered laser light and it has been extensively documented as a unique approach to treating cancer with exceptional selectivity. Gold nanoparticles play a crucial role in photothermal applications due to several advantageous properties[10].

Zinc Oxide Nanoparticles (ZnO NPs)

- Broad-spectrum antibacterial properties.
- Role in keratinocyte proliferation and wound re-epithelialization.

Zinc oxide nanoparticle has significant works due to their extraordinary antimicrobial, anti- inflammatory, and regenerative properties. Zinc oxide is anall-purpose material which have been widely used in various biomedical applications which have its own biocompatibility and which have a ability to interact with biological systems at the nanoscale[13]. Zinc is important element for functioning of a wide range of physiological functions of living organism. Zinc has anti – inflammatory properties. Zinc is necessary element for our health and ZnO Nanoparticles (NPs) and have a good biocompatibility with human cells[14].

Copper Oxide Nanoparticles (CuO NPs)

- Angiogenic and antimicrobial properties.
- Potential cytotoxicity concerns and optimization strategies.

Polymeric Nanoparticles
Chitosan Nanoparticles

- Synergistic effect with alginate in wound healing.
- Controlled drug delivery and antimicrobial properties.

Nanoparticles can be combined with other material such as chitosan and alginate to induced a higher efficacy and by producing a synergistic therapeutic effect. A combined chemotherapy is proposed to induced a higher effectiveness in the treatment by producing a synergistic therapeutic effect.Chitosan is a natural polysaccharide[12] and mostly derived from chitin and a copolymer of glucosamine and N- acetyl – D – glucosamine linked together by β (1,4) glycosidic bonds, and partial deacetylation approach and the deacetylation endowed high amine functional groups to the chitosan backbone which permit strong electrostatic interactions. Chitosan havefavourable biological functionalities e.g. biocompatibility, biodegradability, low, toxicity, haemostatic, bacteriostatic, fungistatic, anticancerogenic and anticholesterolemic, etc.[7]

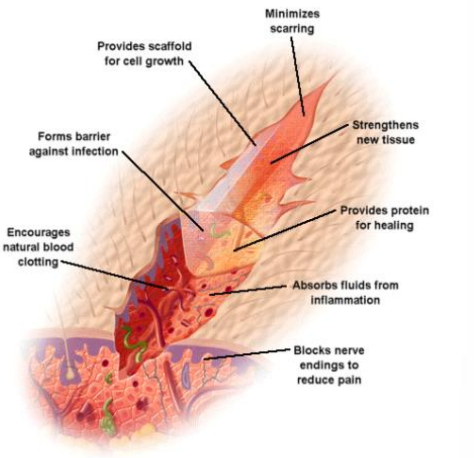
Poly (lactic-co-glycolic acid) (PLGA) Nanoparticles

- Controlled and sustained drug release.
- Application in chronic wound management.

Chitosan is a natural biopolymer that derived from chitin, and a major component of crustacean outer skeletons. This material known in the wound management fields for its haemostatic properties. It also possesses other biological activities and affect macrophage function that helps in faster wound healing. It has an aptitude to stimulate cell proliferation and histoarchitectural tissue organisation. The biological properties including bacteriostatic and fungistatic properties are particularly useful for wound treatment. Flexible, thin, transparent, nivel chitosan- alginate polyelectrolyte complex (PEC) membranes caused an accelerated healing of incision wounds in a rat model compared with conventional gauze dressing. The silver sulfadiazine- incorporated bilayer chitosan wound dressing showed excellent oxygen permeability, controlled water vapour transmission rate and water- uptake capability.

Figure 7: Healing of chronic ulcer wound on first **Figure 8**: Healing of chronic ulcer wound

Patient with the application of chitosan based on second patient with the application of wound dressing[2] chitosan based wound dressing[2]



Chitosan provides a non - protein matrix for 3D tissue growth and activates macrophages for tumoricidal activity. It stimulates cell proliferation and histoarchitectural tissue organization. Chitosan is a haemostat, which helps in natural blood clotting and blocks nerve endings reducing pain[2]**(Figure** 9).

Figure 9: Schematic representation of the benefits of chitosan wound dressing[2]

LIPID-BASED NANOPARTICLES

Solid Lipid Nanoparticles (SLNs)

- Enhanced delivery of hydrophobic drugs.
- Biocompatibility and stability in alginate formulations.

Liposomes

- Encapsulation of bioactive molecules (growth factors, peptides).
- Improved skin penetration and wound healing efficiency.

Carbon-Based Nanoparticles

Graphene Oxide (GO) and Carbon Nanotubes (CNTs)

- Potential for promoting fibroblast proliferation.
- Concerns regarding biocompatibility and cytotoxicity.

MECHANISMS OF ACTION OF NANOPARTICLE-LOADED ALGINATE IN WOUND HEALING

Antimicrobial Activity

- Prevention of bacterial infections in chronic wounds.
- Comparison of NP effectiveness against Gram-positive and Gram-negative bacteria.

Anti-Inflammatory and Antioxidant Effects

- Reduction of oxidative stress in wounds.
- Modulation of inflammatory cytokines (IL-6, TNF-α).

Angiogenesis and Tissue Regeneration

- Role of NPs in promoting endothelial cell proliferation.
- Impact on vascular endothelial growth factor (VEGF) expression.

Controlled Drug Delivery and Sustained Release

- Mechanisms of NP-loaded drug release in alginate matrices.
- Advantages in chronic wound treatment.

FABRICATION TECHNIQUES OF NANOPARTICLE-LOADED ALGINATE DRESSINGS

Electrospinning

- Formation of nanofibrous wound dressings.
- Advantages in high surface-area drug delivery.

Freeze-Drying and Lyophilization

- Enhanced stability of NP-alginate composites.
- Porosity control for improved wound healing.

3D Bioprinting

- Customizable wound dressings with NP incorporation.
- Potential for personalized medicine.
- **Cross-Linking Methods**
- Ionic cross-linking (Ca^{2+}, Ba^{2+}).
- Covalent cross-linking for stability enhancement.

APPLICATIONS OF NANOPARTICLE ALGINATE IN WOUND HEALING

- Treatment of chronic wounds (diabetic ulcers, pressure ulcers, venous ulcers).
- Management of burn wounds. - Prevention of microbial infections.
- Role in post-surgical wound care.
- Tissue engineering and skin regeneration

CHALLENGES AND LIMITATIONS

1. Stability and Aggregation of Nanoparticles
    - Issues with long-term storage and NP dispersion.
2. Cytotoxicity and Biocompatibility Concerns
    - Safety assessments of NP-alginate formulations.
3. Scalability and Cost-Effectiveness
    - Challenges in large-scale production.
4. Regulatory and Clinical Approval Challenges

- FDA and EMA guidelines for NP-based dressings.

Restoration of tissue continuity after injury is a natural phenomenon, infection, quality of healing, speed of healing, fluid loss and other complications that enhance the healing time represents a major clinical challenge. Delayed healing is generally a result of compromised wound physiology and typically occurs with venous stasis, diabetes or prolonged local pressure. Second major challenge is prevention of scarring, keloid formation or contractures and a cosmetically acceptable healing[2].

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

1. Smart and Stimuli-Responsive Alginate-NP Dressings
   - pH-responsive and temperature-sensitive wound dressings.
2. Combination Therapies with Growth Factors and Stem Cells
   - Potential in regenerative medicine applications.
3. Artificial Intelligence (AI) and Machine Learning for Wound Care
   - Predictive modelling for optimized NP-alginate formulations.

The antimicrobial activity of silver has been used for many years and literatures shows that in small concentration and it considered as safe for human use[6]. Cao Y et.al aims to fill these gaps by introducing the critical role of immune regulation in the wound healing process and systematically reviewing biomaterials targeting immune modulation and their mechanisms. These will provide a foundational understanding and guidance for future research in wound healing and related materials science fields. These paper highlights recent advancements and future prospects in biomaterials for wound healing via immunomodulatory with a focus on emerging biomaterials and their less – explored immunomodulatory mechanism such as mitochondrial grafts, biomaterial morphology, metal ions, and composites and these insights present promising avenues for future research in wound healing which offering valuable direction and inspiration for further study in this field[3].

CONCLUSION

- **Summary of Key Findings**
  - Importance of NP-alginate composites in wound healing.
- **Potential Impact on Future Wound Care Strategies**
  - Role in personalized medicine and next-generation wound dressings.
- **Recommendations for Further Research**
  - Addressing current challenges and regulatory advancements.

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