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Review Article

Bioadhesive Solid Lipid Nanoparticle-Loaded Hydrogels for Wound Healing: Formulation Strategies, Therapeutic Potential and Recent Advances

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ABSTRACT

Wound healing is a coordinated biological process that can be impaired by infection, persistent inflammation, oxidative stress, poor tissue hydration and inadequate local drug exposure. Conventional topical dosage forms may suffer from rapid removal from the wound surface, uncontrolled drug release and limited residence time. Bioadhesive hydrogels and solid lipid nanoparticles (SLNs) provide complementary approaches to these limitations. Hydrogels can maintain a moist wound environment and conform to irregular wound surfaces, while bioadhesive polymers can prolong contact with tissue. SLNs can protect incorporated drugs, modulate release and provide a versatile platform for topical delivery. Combining SLNs with a bioadhesive hydrogel therefore offers a rational strategy for prolonged and localized wound therapy. This review discusses wound healing, limitations of conventional topical systems, SLN fundamentals and formulation, bioadhesion mechanisms, polymers used in bioadhesive hydrogels, and strategies for integrating SLNs into hydrogel matrices. Particular attention is given to metronidazole as a locally delivered antimicrobial agent relevant to infected or anaerobe-associated wounds, while distinguishing direct evidence from broader platform evidence. Recent experimental studies involving SLN-hydrogel and adhesive hydrogel systems are critically compared with respect to particle size, entrapment efficiency, release behaviour, antimicrobial activity, tissue adhesion and wound-healing outcomes. Formulation and evaluation considerations, stability, scale-up, translational barriers and future research directions are also addressed. The combined platform is promising, but stronger standardized in vivo and clinical evidence is required before broad therapeutic translation.

INTRODUCTION

Wound healing is a dynamic process involving haemostasis, inflammation, proliferation and

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remodelling. Disruption of the normal sequence by microbial contamination, persistent inflammation, oxidative stress or impaired vascularization can delay closure and increase the risk of chronic wounds. Topical drug delivery is attractive because it can place the active ingredient close to the wound bed while reducing unnecessary systemic exposure. Nevertheless, exudate, movement and repeated dressing changes can shorten residence time and reduce effective drug exposure.

Hydrogels are particularly useful in wound management because their hydrated polymeric networks can absorb or retain water and conform to tissue. Bioadhesive hydrogels add the ability to interact with biological surfaces through hydrogen bonding, electrostatic interactions, van der Waals forces, hydrophobic interactions or other interfacial mechanisms. Recent hydrogel literature describes bioadhesion as an important strategy for prolonging local drug administration and improving contact with soft tissues. [1,2]

SLNs are colloidal carriers composed primarily of a solid lipid matrix stabilized by surfactants. Their potential advantages include protection of incorporated drugs, controlled release, occlusive effects on skin and the ability to be incorporated into semisolid dosage forms. However, conventional SLN dispersions can have low viscosity and may require incorporation into a gel for convenient topical administration. [3–5]

A bioadhesive SLN-loaded hydrogel combines these functions: the nanoparticle provides a drug-carrier microenvironment, whereas the hydrogel provides application properties, hydration and prolonged residence. This review focuses on the formulation logic and therapeutic evidence for this combined platform, with metronidazole considered as a relevant topical antimicrobial example.

2. WOUND HEALING AND THE NEED FOR ADVANCED TOPICAL DELIVERY

2.1 Phases of wound healing

The healing response begins with haemostasis, followed by an inflammatory phase in which immune cells remove debris and microorganisms. The proliferative phase involves re-epithelialization, fibroblast activity, extracellular-matrix deposition and angiogenesis. Remodelling subsequently reorganizes collagen and strengthens repaired tissue. Prolonged inflammation or persistent infection can interfere with these stages and produce delayed or non-healing wounds.

2.2 Challenges in topical wound therapy

Topical formulations must remain at the wound site despite exudate and mechanical disturbance. They should release drug at an appropriate rate, avoid excessive irritation, maintain acceptable rheological properties and permit practical application. An effective dressing may additionally require antimicrobial activity, moisture management, oxygen exchange, mechanical protection and biocompatibility.

3. HYDROGELS FOR WOUND MANAGEMENT

Hydrogels are three-dimensional polymer networks capable of retaining substantial quantities of water. In wound care they can maintain hydration, conform to tissue and serve as reservoirs for drugs or nanoparticles. Recent reviews in *IJPS Journal* also describe adhesive and semisolid hydrogels as systems capable of prolonged drug administration. [2]

3.1 Bioadhesive hydrogels

Bioadhesion refers to the attachment of a formulation to a biological surface. Depending on



the polymer and tissue environment, adhesion can involve hydrogen bonding, electrostatic attraction, interpenetration of polymer chains and hydrophobic or van der Waals interactions. A useful bioadhesive system must balance adhesion with ease of removal, because excessive adhesion can damage newly formed tissue.

3.2 Polymers relevant to bioadhesive hydrogels

Carbopol and chitosan are frequently investigated for bioadhesive drug delivery. Carbopol provides high viscosity and strong polymer–tissue interactions, while chitosan can contribute bioadhesion, film formation and antimicrobial-related functionality. Other hydrogel-forming materials include alginate, gelatin, cellulose derivatives, hyaluronic acid and synthetic polymers. Selection depends on pH, cross-linking behaviour, mechanical strength, drug compatibility and desired residence time.

4. SOLID LIPID NANOPARTICLES

SLNs are lipid-based colloidal carriers in which the dispersed lipid remains solid at physiological and room temperatures. A typical formulation contains a solid lipid, surfactant and aqueous phase. The lipid matrix can accommodate active pharmaceutical ingredients while the surfactant stabilizes the dispersed particles. Modern reviews continue to describe SLNs as versatile carriers for topical and transdermal delivery. [3–5]

4.1 Composition

Common lipid classes include triglycerides, partial glycerides, fatty acids, steroids and waxes. Surfactants influence particle formation and stability, while co-surfactants or charge modifiers may be introduced when required. Glyceryl monostearate (GMS) is a commonly investigated solid lipid for topical nanoparticle systems because

it provides a solid matrix suitable for controlled release.

4.2 Preparation approaches

SLNs can be prepared by high-pressure homogenization, ultrasonication, microemulsion, solvent evaporation, solvent diffusion and related techniques. Process choice affects particle size, polydispersity, drug incorporation and residual-solvent considerations. The quasi-emulsion solvent diffusion approach can be useful when formulation components require an organic phase followed by diffusion and nanoparticle formation.

4.3 Critical formulation variables

Lipid concentration, surfactant concentration, drug-to-lipid ratio, organic-to-aqueous phase ratio, mixing intensity, sonication and temperature can alter nanoparticle characteristics. Excessive surfactant may increase irritation risk or destabilize the system, whereas insufficient surfactant may promote aggregation. Optimization should therefore consider particle size, PDI, zeta potential, entrapment efficiency and release rather than a single response.

5. SLN-HYDROGEL SYSTEMS FOR TOPICAL DELIVERY

Although SLN dispersions can improve drug localization, their low viscosity may limit direct application to wounds. Incorporation into a hydrogel can increase residence time, improve spreadability and provide a convenient semisolid dosage form. Recent *IJPS Journal* literature similarly notes that SLN dispersions are often incorporated into gels or ointment-like systems for dermal administration. [4,5]

The combination can create complementary release controls. Drug partitioning from the lipid matrix can slow release, while diffusion through



the hydrogel network adds a second barrier. The final profile depends on lipid crystallinity, drug affinity for the lipid, polymer concentration, cross-link density, hydration and nanoparticle distribution within the gel.

6. BIOADHESIVE SLN-LOADED HYDROGELS

A bioadhesive SLN-loaded hydrogel can be conceptualized as a multi-level delivery system: the active ingredient is associated with the SLN, the SLN is dispersed through the hydrogel, and the hydrogel interacts with wound tissue. This architecture may reduce rapid wash-off and create a sustained local microenvironment. The concept is particularly attractive for antimicrobial therapy where prolonged exposure at the wound surface may be desirable.

6.1 Mechanistic advantages

Bioadhesion may increase residence time; the hydrated matrix may support a favourable wound environment; the lipid carrier may protect the drug and modulate release; and the combined formulation may improve handling compared with a low-viscosity nanoparticle dispersion. These advantages are formulation-dependent and should be demonstrated experimentally rather than assumed.

6.2 Potential limitations

The combined system introduces additional variables. Nanoparticle aggregation during gel incorporation, changes in particle size, drug leakage, polymer-surfactant interactions and changes in rheology can occur. The final gel must therefore be characterized after nanoparticle incorporation, not only at the SLN stage.

7. METRONIDAZOLE AS A TOPICAL ANTIMICROBIAL CANDIDATE

Metronidazole is an antimicrobial agent with established activity against anaerobic microorganisms and has been used in local formulations where anaerobic microbial involvement is relevant. A metronidazole-loaded hydrogel system has previously been investigated for wound dressing, with controlled release and antimicrobial performance reported in an experimental model. [6]

Lipid-based delivery can provide another route for modifying local exposure. A metronidazole-loaded SLN gel has been reported for buccal delivery, demonstrating the feasibility of combining metronidazole with SLNs and a polymeric gel, although this evidence should not be interpreted as direct proof of wound-healing efficacy. [7] Metronidazole-loaded lipid microparticles incorporated into polymeric hydrogels have also been investigated for improved skin localization, providing supportive evidence for the topical lipid-carrier/gel concept. [8]

These findings provide a rational formulation basis for studying metronidazole in a bioadhesive SLN-loaded hydrogel for wound applications. Direct evidence specific to the exact metronidazole-GMS-bioadhesive hydrogel combination remains limited and should be established through formulation, antimicrobial and wound-healing studies.

8. EVIDENCE FROM SLN-HYDROGEL AND ADHESIVE WOUND SYSTEMS

Evidence from other active ingredients supports the platform concept. Curcumin-loaded SLN hydrogel systems have shown controlled release, antimicrobial or antibiofilm effects and improved experimental wound healing. [9] Astragaloside IV-loaded nanoparticle-enriched hydrogels have demonstrated sustained topical delivery with



favourable wound-healing outcomes in experimental models. [10] A lacticin 3147 SLN hydrogel has been investigated against wound-associated bacteria including *S. aureus* and MRSA, illustrating the potential of SLN hydrogels as local antimicrobial systems. [11]

Independent bioadhesive hydrogel studies further support the importance of adhesion and multifunctionality. Antibacterial and antioxidative adhesive hydrogels have been developed to remain associated with wounds while supporting healing, and injectable bioadhesive hydrogels have demonstrated antibacterial and wound-healing activity in experimental models. [12,13] These studies do not establish equivalence with an SLN-metronidazole hydrogel, but they help define desirable performance characteristics.

9. FORMULATION AND EVALUATION

9.1 Preformulation

Drug–excipient compatibility can be investigated using FTIR, while UV spectrophotometry can support quantitative assay development. Solubility, melting behaviour and partitioning information may guide selection of lipid and surfactant.

9.2 SLN characterization

Particle size and PDI describe dispersion characteristics, while zeta potential provides information about surface charge and colloidal stability. Entrapment efficiency and drug loading quantify incorporation. Morphological examination can provide complementary structural information.

9.3 Hydrogel characterization

The final gel should be evaluated for appearance, pH, viscosity, spreadability, drug content, swelling

or water retention where relevant, and bioadhesive strength. Drug release should be studied using a suitable membrane and receptor medium.

9.4 Antimicrobial evaluation

Antimicrobial testing should use organisms selected to match the intended indication and should include suitable controls. Zone-of-inhibition studies provide screening information, whereas quantitative bacterial reduction assays can better characterize performance.

9.5 Wound-healing evaluation

Ethically approved in vivo wound models can assess wound contraction, epithelialization, histopathology, collagen organization, inflammatory response and microbial burden. Wound closure alone is insufficient evidence of antimicrobial efficacy for an infected-wound product.

10. FORMULATION OPTIMIZATION

Design of Experiments can reduce the number of experimental runs while evaluating interactions among formulation variables. For an SLN system, lipid and surfactant levels may be independent variables, while particle size, entrapment efficiency and zeta potential can serve as responses. For the subsequent hydrogel, polymer concentration and nanoparticle loading can be optimized against viscosity, adhesion, release and spreadability. A desirability-based approach can identify a formulation that balances multiple responses rather than maximizing a single property.

11. ADVANTAGES AND LIMITATIONS

Potential advantages include prolonged residence, controlled drug release, improved topical localization, protection of incorporated drug,



convenient application and formulation flexibility. Limitations include nanoparticle aggregation during gel incorporation, drug leakage, changes in rheology, physical instability, microbial contamination of aqueous gels and possible differences between laboratory and clinical wound conditions.

12. STABILITY, SCALE-UP AND TRANSLATIONAL CONSIDERATIONS

Lipid polymorphism, drug expulsion, particle aggregation and viscosity changes can affect stability. Long-term studies should monitor particle size, PDI, zeta potential, drug content, release and microbial quality. Scale-up may alter mixing and energy input and therefore must be linked to critical quality attributes. Translational development requires reproducible manufacturing, safety assessment and clinically relevant comparative efficacy.

13. RECENT ADVANCES AND FUTURE PERSPECTIVES

Future systems may combine bioadhesion with stimuli-responsive release, antimicrobial peptides, antioxidants, angiogenic agents or smart wound-

monitoring functions. Multifunctional hydrogels increasingly respond to wound pH, reactive oxygen species or enzymes. For metronidazole systems, future research should determine whether bioadhesion and SLN incorporation improve local antimicrobial exposure enough to justify the added formulation complexity compared with conventional topical metronidazole gels.

14. CRITICAL APPRAISAL

The literature supports each component of the proposed platform individually, but direct evidence for a metronidazole-loaded bioadhesive SLN hydrogel for wound healing remains comparatively limited. Evidence from curcumin, astragaloside IV, lacticin 3147 and other actives demonstrates the feasibility of SLN-hydrogel delivery, whereas metronidazole-specific studies support the drug's compatibility with hydrogel or lipid-based local delivery. The research opportunity is therefore to determine whether the combination of metronidazole, a suitable solid lipid and a bioadhesive polymer produces measurable advantages in retention, antimicrobial activity and wound repair.

TABLE 1. Representative evidence relevant to SLN, hydrogel and bioadhesive wound delivery

System/active	Delivery concept	Key relevance	Evidence
Metronidazole alginate hydrogel	Drug-loaded hydrogel	Controlled release and antimicrobial/wound-dressing rationale	Experimental
Metronidazole-loaded SLN gel	SLN + polymeric gel	Feasibility of metronidazole lipid nanoparticle gel delivery	Experimental; buccal
Metronidazole lipid microparticle hydrogel	Lipid carrier + hydrogel	Skin localization and local delivery rationale	Ex vivo
Curcumin SLN hydrogel	SLN + hydrogel	Controlled release, antimicrobial and wound-healing evidence	Experimental
Astragaloside IV nanoparticle hydrogel	Nanoparticle-enriched hydrogel	Sustained topical delivery and wound healing	Experimental
Lacticin 3147 SLN hydrogel	SLN + antimicrobial hydrogel	Activity against wound-associated bacteria	Ex vivo/experimental
Bioadhesive antibacterial hydrogels	Adhesive polymer network	Longer wound residence and antibacterial activity	Experimental



TABLE 2. Suggested critical quality attributes

Stage	Parameter	Purpose
SLN	Particle size/PDI	Assess colloidal dispersion
SLN	Zeta potential	Assess surface charge and stability
SLN	Entrapment efficiency/drug loading	Quantify drug incorporation
SLN	Morphology	Assess particle structure
Hydrogel	pH/viscosity/spreadability	Assess topical acceptability
Hydrogel	Bioadhesive strength	Assess tissue residence potential
Final system	In-vitro release	Characterize release kinetics
Final system	Antimicrobial activity	Assess biological performance
Final system	Stability	Assess changes during storage

15. CONCLUSION

Bioadhesive SLN-loaded hydrogels represent a rational multifunctional platform for topical wound management. SLNs can provide a controlled-release lipid carrier, while bioadhesive hydrogels can improve residence and application characteristics. Metronidazole offers a relevant antimicrobial payload for selected wound infections, and existing literature provides supportive evidence for metronidazole in hydrogel and lipid-based delivery systems. Nevertheless, direct evidence for the complete platform remains limited. Future work should emphasize standardized comparative studies, long-term stability, safety, scale-up and clinically relevant wound models.

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