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Article

A Decision Framework for Removable Hydrogel Interfaces in Traumatic Amputation Care

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Abstract: Traumatic amputation wounds require multiple evaluations and debridement before final closure. Therefore, the temporary hydrogel interface needs to provide effective short-term coverage and be convenient for subsequent examinations. This study proposes a decision-making framework using oxidized alginate-carboxymethyl chitosan containing silver nanoparticles (OAlg-CMCS/AgNP) as an illustrative candidate. This framework first determines whether the currently clinically acceptable dressings can meet specific requirements, and then considers factors such as dressing placement and fixation, planned removal and early removal, material recovery, and biocompatibility. The initial contact time is set at 24 hours to align with the early clinical assessment. This duration serves as the time frame for the initial test and further evaluation of its safety is required. If the adhesive effect of the material is limited, the wound coverage rate will be used as the primary evaluation metric and compared with the pre-defined control group of simple dressings. For candidate materials without silver, after completing the qualification assessment of the evaluation matrix and operation procedures, they can enter the next stage. The silver-containing materials need to be further tested for their antibacterial effects and impact on cells, and the influence of processing and aging on the material properties should also be examined. This framework specifies how material coverage, recovery, silver exposure, procedural safety, and wound inspectability should be assessed through five decision rules (DR1–DR5) to guide subsequent development decisions. The test results will also provide a basis for subsequent material improvement and research decisions.

Keywords: hydrogel; traumatic amputation; combat wound; removable wound interface; oxidized alginate; carboxymethyl chitosan; silver nanoparticles

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1. Introduction

Extremity trauma is common in modern conflict. Reports from Operations Iraqi Freedom and Enduring Freedom indicate that blast injuries are often accompanied by wound contamination, tissue necrosis, vascular damage, fractures, and extensive soft tissue defects [1,2]. Amputees also face a higher risk of wound infection. A study of 1,271 combat-related open limb injury patients found that among those with the most severe injuries, 100 cases (47%) developed wound infections in the early stages of hospitalization. In contrast, 66 cases (14%) of open fracture patients and 12 cases (3%) of open soft tissue injury patients experienced infection [3]. The pathogens in the wounds can also change as the patients are evacuated and hospitalized, possibly related to initial contamination, subsequent surgeries, the use of antibacterial drugs, and the hospital environment [4,5]. These circumstances indicate that appropriate temporary covering methods are needed for amputated wounds between different treatment stages, while also leaving space for subsequent handling.

Traumatic amputations usually require staged treatment. The Joint Trauma System (JTS) guidelines recommend keeping the wound open after the first surgery and repeatedly rinsing and debridement based on the extent of tissue damage, and closing the wound only when the wound condition is clear [1,6]. Within 24 hours after surgery, medical staff also need to be able to inspect and handle the wound at any time [1]. Negative-pressure wound therapy (NPWT) can be used for wounds that have partially completed debridement, preparing for subsequent closure, skin grafting, or flap coverage, and can also be used for wound management during air medical transport [1,7–12]. This article focuses on hydrogels that are mainly used for temporary coverage after surgical preparation, which need to be easy to remove to facilitate subsequent inspection and treatment.

Current hydrogel research mostly focuses on their adhesion, antibacterial effect, and ability to promote wound healing. However, amputated wounds often require repeated inspection and debridement, and the actual effectiveness of the material also depends on whether it can be conveniently placed and removed. Strong adhesion helps fix the hydrogel, but it may increase the difficulty of removal; the material remaining for too long may also hinder wound inspection. In addition, the antibacterial components, when inhibiting bacteria, may also affect the cells involved in tissue repair. Therefore, when designing such hydrogels, it is necessary to balance the wound coverage effect with the convenience of subsequent care.

The framework proposed in this study assesses hydrogels from three aspects: clinical use, material application and removal, and the impact on local tissues. The material formulation, application method, and removal process are examined as a whole. The polymer concentration affects the mechanical properties and drug release of the material, while the contact time between the material and the wound influences the mechanical effect and biological response. Therefore, when comparing different formulations, actual nursing conditions need to be considered for evaluation.

This study selected the OAlg-CMCS/AgNP hydrogel as the research object to analyze the relationship between material performance and biological response. The aldehyde groups on OAlg can react with the amino groups on CMCS to form imine bonds, enabling the material to form a hydrogel without the need for additional small molecule crosslinking agents [13,14]. Previous studies have explored the application of this polymer combination in cell delivery and wound healing [13–17]. Additionally, studies using oxidized dextran, CMCS/polyethyleneimine, or oxidized konjac glucomannan have provided other evidence related to polymer networks [18–20]. Adding AgNP can enhance the antibacterial effect of the material, and its effect and impact on mammalian cells depend on the release rate of silver, particle state, and testing environment [21–30]. Based on this, the proposed framework considers how material coverage and antibacterial performance can be evaluated alongside the requirements of wound care.

The researchers collected clinical guidelines, material research, and relevant testing standards through literature search to provide a basis for the formulation of the decision framework, and organized relevant evidence according to polymer composition, research model, and evaluation indicators. On September 11, 2026, researchers conducted a PubMed search up to that date. The first group of searches focused on the title and abstract, combining hydrogel-related terms with oxidized alginate, alginate dialdehyde, and CMCS, etc. The second group of searches focused on the application of hydrogels in wounds, burns, and dressings, and combined keywords such as removable, soluble, on-demand release, and controlled dissolution, covering different types of polymers. Appendix A records the exact search strategies, retrieval counts, and selection notes.

After the search, the researchers first reviewed the titles, then read the relevant abstracts, focusing on the removal method of the material, as well as the dissolution or detachment phenomena reported in the studies, and further paying attention to the adopted wound model. The representative studies retained mainly involved materials with a chemical composition similar to CMCS or provided relevant evidence for the removal method and wound application. Studies focusing solely on stimulus-controlled

drug release were not treated as evidence of dressing removal. The above literature, together with clinical guidelines and testing standards, formed the evidence base of the framework and provided references for the formulation of five decision rules. These rules are used to guide subsequent tests and material screening, and their applicability still needs to be confirmed through further verification. Additional search and selection details, including source-access limitations, are documented in Appendix A.

2. Intended Use and Clinical Boundary

2.1. Proposed Intended-Use Statement

This product is a temporary conformal interface designed for wound care after hemostasis, thorough debridement, and irrigation in traumatic amputation surgeries. It should be used in secondary or tertiary medical institutions with the necessary conditions, covering standard secondary dressings, and removed during the next scheduled follow-up. The product should be capable of being prepared using the existing equipment of the target medical institution, and is mainly used for short-term wound coverage and adhesion during the transfer of injured personnel or post-operative care. According to the relevant guidelines for early re-examination and wound and dressing inspection [1, 6, 31] (Section 2.4), the proposed initial validation interval is set at 24 hours.

2.2. Explicit Exclusions

For wounds that are still bleeding, require immediate closure, or lack professional supervision, corresponding surgical treatment should be given priority. During the use of this interface, debridement, rinsing, and infection treatment still need to be carried out in accordance with clinical standards [1, 6, 32]. Additionally, the wound surface also needs to be covered with matching dressings to provide necessary protection.

Silver is to reduce bacteria on the wound surface during contact. Its effect mainly focuses on local bacterial control. The occurrence and development of combat-related infections are related to factors such as the degree of injury, pathogens, repeated surgeries, antibiotic use, transfer of injured personnel, and host condition [3–5]. Studies on osteomyelitis after combat-related open tibial fractures [33] can provide reference for related assessment, and the application effect of silver-based hydrogel in traumatic amputation wounds still needs to be confirmed through specialized research.

2.3. Comparator Hierarchy

The proposed comparison is between the hydrogel-containing dressing system and the same dressing system without hydrogel. Before testing, clinical reviewers should determine the wound contact layer, absorbent dressing, and fixation method used in both groups, and clarify whether filling wound recesses is necessary. Both groups should follow the same care process, and the use of the dressing alone should be a clinical plan suitable for the target wound. If the contact layer or filling method needs to be adjusted after adding hydrogel, these changes should be recorded to evaluate the effect of the entire system.

For traumatic wounds that have undergone adequate debridement, NPWT remains an important clinical reference plan and can also be used for wound management during air medical transportation [1, 7–12]. If a passive covering method is chosen clinically, the reviewers should clarify which needs in the existing dressing care have not been met. For example, if the clinical requirement is for the material to remain adhered during care, the wound coverage effect can be used as a relevant evaluation indicator. Researchers should determine the main evaluation indicators based on specific clinical issues before formal validation.

2.4. Rationale for a 24-Hour Initial Validation Interval

The JTS guideline suggests that wounds should be re-evaluated within 24 hours after the first amputation or debridement. For stable conditions without signs of infection or disease progression, the use interval of NPWT can be extended to 48–72 hours [1]. Therefore, 24 hours was chosen as the initial test duration for this study to evaluate the

performance of the material and provide a basis for subsequent checks. This duration cannot directly be used as the safe usage time limit for OAlg-CMCS/AgNP. The material recovery rate and biological activity assessment proposed in Sections 4-5 will also use this time range. If the antibacterial effect only appears in longer-term tests, it will need to be further verified whether it is applicable to the short-term contact scenario set by this study.

3. Clinical Requirements for Placement and Removal

During the initial surgery, tissues that were determined to be viable may gradually show signs of necrosis during the subsequent healing process [1, 6]. After the interface is removed, the surgeon needs to examine the color, odor, exudate, bleeding, and layering of the tissue. The material should maintain good contact with the wound surface, be convenient for subsequent examination and removal, and minimize additional handling of the tissue to avoid prolonging the rinsing time or increasing the debris cleaning workload due to material adhesion.

Even if the gel is extruded and it can regain its original shape, this does not mean that it can be completely removed. When removing it, the gel may stick to the tissue again and cause rupture, especially in deeper wound depressions. The key point is that the material should remain stable during the process of covering the wound, and be easily removable when needed. At the same time, it should minimize the residue of the material, the force and time required for removal, as well as the impact on the surrounding tissues. Section 4.3 will introduce the specific testing methods.

The movement and position changes of the injured person may cause the gel to shift. The fixation method of the outer dressing also affects the adhesion of the gel to the wound. To evaluate dressing performance during transport, the proposed test would compare the gel-containing dressing with the dressing-only system using the same fixation method. A matched silver-free hydrogel group would also be included. These comparisons would assess the effects of AgNP addition on material performance.

The two-component formulation needs to be stored separately before use, and mixed in the prescribed proportion during use to ensure a stable dosage each time. The tests should closely simulate the actual usage process, such as operating with gloves on, and observing whether the material can still function properly after storage. It is also necessary to check if the mixed material will solidify prematurely in the syringe and whether the change in the proportion of the two components affects the usage effect. These issues may be difficult to detect in routine laboratory tests, so they need to be evaluated based on actual operating conditions. Table 1 summarizes the main requirements in clinical use, material performance, biosafety, and production, and explains the inspection methods and judgment bases for each requirement.

Table 1. Requirements and Measurements for a Temporary Hydrogel Interface.

Requirement	Required condition	Measurement and interpretation
Clinical-use	Post-hemostasis and post-debridement use; open wound remains accessible; planned removal within 24 h.	Workflow simulation and clinician review. Reject if application delays care, obstructs inspection, or conflicts with serial debridement.
System comparator	Hydrogel must add value beyond a clinically acceptable, prespecified dressing-only system.	Compare 24-h contact coverage using matched surface and scoring rules. Report dressing layers, packing, leakage, and pooling; burden and inspectability impose independent limits.
Material-performance	Workable mixing and gelation; conformal retention during motion	Measure gelation, rheology, transport challenge, mass change, leakage, and

	and exudate; controlled swelling and erosion.	batch variability under intended-use conditions.
Recoverability	Recovery at the planned assessment and at an earlier access challenge, within limits for force, time, residue, and tissue disturbance.	Specify lifting and irrigation. Measure polymer or validated-tracer recovery, residual coverage, removal force and time, and tissue damage.
Biological-exposure	Acceptable matrix and leachable responses for every candidate; paired antibacterial and cell-response acceptance when silver is included.	Direct-contact and extract tests for the matrix. Pair antimicrobial and cell tests at measured exposure; apply DR3 qualification, bounded retesting, and stopping rules.
Manufacturing and storage	Sterile, reproducible two-component delivery with stable polymer and particle state.	Repeat identity, gelation, mechanics, particle characterization, and release after sterilization and aging.

4. Material Performance and Recovery

4.1. Evidence for Dynamic Networks and Removable Interfaces

Previous studies have shown that OAlg-CMCS can form hydrogels and has the potential for cell delivery and wound healing. Mohabatpour et al. used this material for cell delivery in in vitro enamel regeneration [13]. Xu et al. used an alginate dialdehyde-CMCS hydrogel to deliver rabbit limbal stem cells to corneal alkali-burn wounds [14]. Other studies have also explored the application of this material combination in wound healing [15–17]. These results provide a reference for the application of the material, but whether the hydrogel can be removed smoothly in deeper and irregularly shaped wounds still requires further testing. For amputated wounds that require multiple debridements and examinations, whether the material can be removed and whether it affects tissue examination after removal are important evaluation contents.

Other studies have also attempted various gel formulations, including CMCS/oxidized dextran/sodium alginate [18], CMCS/PEI [19], and a composite material composed of oxidized konjac glucomannan, dopamine- and cysteine-modified poly(glutamic acid), and polylysine [20]. These studies helped researchers understand the adhesion of the gel to the tissue and its impact on the tissue, and also provided references for subsequent tests. Due to the different compositions and structures of various gels, it still needs to be determined through specialized tests whether the OAlg-CMCS gel can be completely removed.

Huang et al. studied a CMCS gel connected to DACNC through dynamic Schiff bonds and used amino acid solutions to dissolve it as needed in a deep partial-thickness burn model [34]. This study demonstrated that specific solutions could assist in the dissolution of the gel. Since the composition and dissolution method of this material are different from those of the OAlg-CMCS gel and the saline-assisted removal scheme used in this study, its actual removal effect still needs to be tested separately.

Cook et al. studied a gel composed of PEI and polyethylene glycol (PEG), and promoted its dissolution by adding cysteine methyl ester [35]. Under conditions of pH 8.6 and 0.3 M cysteine methyl ester, the formulation selected for animal testing reached a rheological dissolution endpoint after approximately 30 minutes. This indicates that the state of the gel has changed. Further examination is needed to check if any material remains in the tissue to understand the actual clearance effect. The study also evaluated the dressing change and healing of pig second-degree burn wounds. Compared with traditional dressings, the histological differences did not reach a statistically significant level, and this result still needs to be judged based on other evidence [35]. Therefore, when evaluating hydrogels, it is necessary to separately examine whether the material has dissolved, whether it can be completely removed, and whether there is still material deposition on the wound surface (see Section 4.3).

If a chemical dissolution method is used, the required solution concentration, pH value, dosage, and contact time for the specific formulation need to be determined, and the degree of material removal should be evaluated. For the OAlg-CMCS/AgNP hydrogel proposed in this study, it is necessary to investigate whether the material can be cleaned up completely and whether it is convenient for doctors to continue checking and treating the wound after removal. These issues need to be further confirmed through subsequent experiments. Table 2 summarizes the main results of existing studies, their reference value for this study, and the tests that still need to be conducted, to facilitate understanding of the basis provided by the existing research.

Table 2. Representative Evidence for Hydrogel Function, Removal, and Translation to Staged Traumatic Amputation Care.

Source and context	Reported finding or scope	Framework implication	Unresolved for this use
JTS amputation guidance [1]	Open management, repeated debridement, and early reassessment.	Initial 24-h test interval; repeated access takes priority under DR5.	Guidance does not validate hydrogel residence or removal.
OAlg-CMCS polymer-pair studies [13-17]	Cell-delivery and wound-repair applications in different formulations and models.	Supports selecting the chemistry for matrix screening under DR2.	Recovery from deep recesses after residence and motion requires direct testing.
Fang et al., CMCS/PEI [19]; fibroblast and rat skin-wound models	Composition-dependent adhesion and cell responses; skin-wound repair was evaluated.	Assess handling and cell effects in the same candidate.	Different polymer network; wound closure does not establish repeat access.
Sun et al., OKPP hydrogel [20]; in vitro assays and infected mouse burns	Injectability, self-healing, adhesion, antibacterial activity, and wound repair were evaluated.	Separates evidence on material functions from the proposed retrieval requirement.	Different network and wound model; staged amputation recovery remains untested.
Huang et al. [34]; CMCS/DACNC; deep partial-thickness burns	Dynamic Schiff-base network; removal triggered by an amino acid solution.	Specify the dissolution trigger and assess the resulting tissue exposure.	Different aldehyde-bearing component; traumatic-cavity clearance and inspection need validation.
Cook et al. [35]; PEI/PEG; porcine second-degree burns	Cysteine methyl ester cleaves thioesters; dressing changes and healing evaluated.	Test dissolution time and conditions together with tissue response.	Burn-model results do not validate deep-cavity residue control or urgent access.
Silver-exposed wound cells and silver dressings [21-25]	Cell and tissue responses depend on the exposure, product, and model.	Pair antimicrobial and cell-response results at measured exposure under DR3.	A biological range must be established for the actual matrix and medium.

DACNC refers to dialdehyde-modified cellulose nanocrystals, PEI refers to polyethyleneimine, and PEG refers to polyethylene glycol. OKPP is composed of oxidized konjac glucomannan, polyglutamic acid modified by dopamine and cysteine, and polylysine. The explanations and unresolved issues related to this study in the table belong to the proposed plan and need to be verified through subsequent experiments.

The rheological tests can help understand the changes of the gel after being subjected to force. For example, observing whether the gel can restore its original state after a large deformation can determine whether it is prone to flow or rupture during use. The test results in the laboratory also need to be combined with the actual usage situation for judgment. Whether the gel can remain on the moist tissue surface and whether it can be kept intact during removal are all related to the entire dressing system. Therefore, tests should be conducted under conditions close to actual usage, and the results should be evaluated comprehensively based on the rheological data. Section 4.3 will introduce the specific evaluation indicators.

4.2. Formulation Variables and Coupled Consequences

The initial experiments will adjust the concentrations of OAlg and CMCS, the proportion of the reaction groups contained in both, and the degree of oxidation of alginate, observing how these changes affect the gel properties. Increasing the reaction groups may cause the gel to form faster and have a more solid structure, but it will also affect water absorption, degradation, the difficulty of removal, residual aldehydes and silver release. These effects need to be determined through experiments. The study can adopt small-scale formulation tests, compare the combinations of different components, and combine the results of material strength, residual aldehydes and cell responses, etc., to select the appropriate formulation. When evaluating, the formation, removal and tissue compatibility of the gel should be considered to ensure that the material can meet multiple requirements in actual use.

After adding AgNP, the performance of the gel will also be affected by the silver content and its release situation. Existing studies have found that when AgNP is added to gel nanocomposites, the flowability and water absorption of the material will change [36]. These results can be used as references, and the specific effects still need to be tested in the OAlg-CMCS system. The internal structure of the gel may affect the stability and release speed of the silver particles, and the chloride and proteins in body fluids will also affect the form of silver after release, such as forming AgCl bound to proteins [37]. Therefore, the formulation research should compare hydrogels without silver with hydrogels containing different amounts of AgNP, observing their performance in operation, adhesion, removal and silver release. If using ionic silver as a control, it is best to match according to the actual silver content released to more accurately compare the effects of different forms of silver. The formulation adjustment may also change the amount of silver release, thereby affecting the amount of silver exposed to cells. Therefore, the material performance and silver exposure situation should be evaluated together, and its biological safety should be further checked in accordance with DR3 requirements.

4.3. Performance Endpoints

The gel needs to have sufficient operational time to fill the irregularly shaped wound gaps and reduce material loss. Before the formal test, experiments should be conducted according to the expected formulation ratio, temperature, ionic concentration, and applicator shape to determine the appropriate operational time. During the tests, observe whether the gel can fully cover the wound and whether the applicator is prone to clogging, and then adjust the formulation or usage conditions accordingly. The determined operational range should also be evaluated in combination with the coverage effect and preparation difficulty described in DR1.

The rheological test can help understand the performance of the gel during force application, flow, and recovery. Strain scanning and frequency scanning can be used to determine the test range for maintaining the stability of the gel structure, while flow curves and yield tests can reflect the flow characteristics of the gel, and step strain recovery tests can observe whether the gel can return to its original state after being deformed by force. These results can help determine whether the gel is easy to move or rupture. The actual usage effect of the gel also needs to be evaluated in combination with the retention situation and removal difficulty in the wound model. If the gel structure

recovers better and the force required for removal is also within an appropriate range, it can meet the requirements of the dressing.

The liquid absorption capacity of the hydrogel dressing needs to be evaluated in conjunction with the entire dressing system. The material should be placed in a test liquid containing proteins and ions for a 24-hour assessment. Mass and dimensions should be measured at defined intervals to assess fluid uptake and swelling. Extractable polymers in the liquid should also be measured to evaluate erosion and material stability. If the gel expanded excessively, was difficult to adhere to the wound, or still had fragments remaining after removal, the formula could be adjusted according to DR2 and Table 3, and ensure that the wound tissue is intact for easier observation by medical staff. For the gel containing silver nanoparticles, attention should also be paid to the release of silver during material decomposition and its contact with the wound tissue. The liquid absorption capacity, wound coverage effect, residual situation after removal, and silver release performance of the gel can all be used together to determine whether it is suitable for wound care.

Table 3. Experimental Decisions for Advancing, Revising, or Discontinuing the Proposed Interface.

Decision rule	Primary endpoint or test	Result or failure condition	Decision
DR1. Incremental value	Primary benefit: 24-h contact-coverage gain versus the defined dressing-only system. Independent limit: preparation and removal burden.	Prespecified confirmatory analysis shows insufficient worthwhile gain, or procedural burden exceeds limits.	Stop if benefit is insufficient or burden excessive. Inconclusive results do not advance; use the prespecified retest plan.
DR2. Removable material window	Retention at 24 h; polymer or tracer recovery, residual coverage, and damage after planned or earlier removal.	Early retention or residue limits fail, while tissue integrity and required inspection remain acceptable.	Adjust and retest. Stop if planned feasible adjustments fail.
DR3. AgNP biological window	24-h viable bacterial reduction paired with viable-cell counts and membrane integrity at measured silver exposure (Section 5.4).	Qualified: all criteria supported at a tested exposure. Failed: every planned feasible exposure clearly fails a criterion. Inconclusive: uncertainty or unresolved assay validity prevents classification.	Qualified: advance to DR4. Failed: end silver branch. Inconclusive: hold and follow bounded retesting; end branch if unresolved (Section 5.4). After ending, remove AgNPs and claim; requalify the silver-free system.
DR4. Exposure control	Matrix performance, cell compatibility, and release profiles across batches, sterilization, aging, and media; measured silver exposure when present.	Processing or use causes a performance or compatibility failure, or shifts silver exposure outside the established biological range.	Correct and retest; stop current candidate if planned corrections fail.
DR5. Inspectability	Required landmark recognition, tissue	A valid test shows obscured required	Stop current candidate at any stage.

and tissue integrity	damage, and repeat access after removal in the irregular tissue-relevant model.	landmarks, blocked repeat assessment, or tissue damage above the acceptance limit.

Whether the gel can be easily removed is an important aspect for evaluating whether it is suitable for wound care. The initial test will gradually increase the force applied during removal and combine with quantitative saline rinsing to observe whether the gel is easily loosened, broken, and whether there is still material residue after removal. Each group of experiments will use the same instrument, withdrawal direction and speed, maximum force, and irrigation volume and duration to compare the performance of different formulations. The cross-linked structure inside the gel helps maintain the shape, but the completeness of the actual removal still needs to be observed through experiments. Whether saline can help the gel loosen and reduce residue will also be determined by the test results. If a chemical dissolution method is subsequently used, the substances released by the material and their impact on the tissue need to be re-evaluated. Before the formal test, unify these operational conditions to help more accurately compare the recovery effects of different candidate materials.

The test should aim to simulate the shape and tissue surface of a real wound, including irregular depressions. If necessary, it can also simulate the situation where muscles are exposed. The test should observe the effect of the gel when it is removed after being placed for 24 hours. It should also consider the situation where clinical examination of the wound needs to be conducted in advance. By comparing the images before and after the gel is placed and recording the time and force required for removal, the impact of the gel on the wound tissue and whether it is convenient for medical staff to continue the examination after removal can be evaluated. According to the DR5 standard, tissue protection and wound visibility are the main evaluation criteria, while the removal efficiency serves as a supplementary indicator.

After the gel is removed, the complete recovered materials, the collected fragments, the materials in the rinsing solution, and the parts remaining on the wound surface should be recorded separately to understand the recovery and residue of the materials. The recovery rate can be calculated based on the initial polymer mass used, or through the verification of a tracer to track the material's whereabouts. When the gel absorbs water, it expands, and when it decomposes, it loses mass. Therefore, simply weighing is difficult to accurately calculate the recovery rate. Combining the residual area on the wound surface and the material content in the rinsing solution, it is possible to more accurately evaluate the removal effect and provide a basis for the DR2 judgment.

4.4. Packaging and Sterilization as Formulation Variables

After sterilization and storage of the hydrogel, its performance may change. Studies have found that gamma-ray irradiation reduces the molecular weight and inherent viscosity of alginate sodium and alters its ability to form a gel [38]. Yuan et al.'s research found that under specific conditions, the gel formation and stability of freeze-dried CMCS after electron beam irradiation remained basically unchanged, and the polymer structure and molecular weight did not change significantly [39]. These results indicate that different materials may have different responses to sterilization treatment, and the silver-containing OAlg-CMCS system still needs to be verified separately. When evaluating the sterilization method, the structure, viscosity, gel-forming ability, strength, particle size, and silver release amount of the materials before and after the treatment should be compared. During storage, silver nanoparticles (AgNP) may gradually aggregate or dissolve, thereby affecting the material performance and silver release [28–30]. Therefore, storage stability tests should also be conducted. The relevant results will be used to determine whether the material needs to be re-evaluated; for the silver-containing formulation, the silver release situation and its potential impact on the tissue should also be re-examined according to DR4 requirements.

5. Silver Exposure and Biological Response

5.1. Antimicrobial Activity Is Exposure-Dependent

The antibacterial effect of silver nanoparticles is related to the silver ions they release and the changes of silver in the surrounding environment. Research has found that under certain conditions, silver ions are the main component that exerts antibacterial effects [26, 27]. Gradual dissolution of silver nanoparticles may increase the toxicity of the material [29], and the size of the particles and their dissolution after entering cells also affect the response of mammalian cells [30]. The proposed release assessment should measure total silver in the same medium used for biological testing. Dissolved silver and particle-associated silver should be quantified separately over time to characterize silver release during the intended contact period.

Traditional media and agar tests are difficult to fully simulate the environment of wound exudate. Proteins and chloride ions in the wound may cause silver to form nanoscale AgCl and form a stable protein layer on its surface [37]. Silver in the wound environment exists in various forms and is influenced by proteins, cells, and tissue debris. The actual exposure level of silver is difficult to determine solely based on the content of free silver ions. The size of the inhibition zone may not accurately reflect the actual antibacterial effect of the material. Therefore, the silver release amount and antibacterial test should use the same wound simulation solution to facilitate the comparison of silver release and antibacterial performance. If the test conditions are different, relevant differences should be recorded to correctly interpret the relationship between the presence of silver and the antibacterial effect.

5.2. Antimicrobial Testing within the Intended-Use Interval

The proposed primary antibacterial endpoint is the change in recoverable viable bacteria after 24 hours of contact, compared with an otherwise identical silver-free hydrogel-dressing system to evaluate the additional antibacterial effect of silver nanoparticles. During the test, the initial bacterial quantity should be recorded and the number of viable bacteria should be continuously tracked to determine whether the bacteria are killed or only their growth is inhibited. Both groups should adopt the same sampling and bacterial recovery methods, and through control experiments, confirm that the neutralization treatment can promptly terminate the antibacterial effect of silver and will not affect the recovery of bacteria [40,41].

After sample removal, residual silver may continue to kill bacteria, resulting in a lower measured number of viable bacteria. Therefore, it is necessary to verify whether the neutralizer can terminate the antibacterial effect of silver according to the ASTM E1054 standard, while ensuring the normal recovery of bacteria [40]. Depending on the research purpose, additional control groups without silver, separate polymers, AgNP dispersion solutions, outer dressings, and silver ions can be added to help distinguish the effects of the dressing as a whole, polymers, and silver, and evaluate the impact of the remaining silver on the test results.

The test bacteria should be selected based on wound infection monitoring data and expected usage scenarios [4,5]. Initially, Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter baumannii can be selected, and other bacteria can be added as needed based on the antibacterial application the material is intended to achieve. The ability to prevent microbial entry and the ability to inhibit biofilm formation belong to different evaluation contents [42,43]. For hydrogel interfaces that are expected to come into contact with the wound for a short period, early biofilm tests should focus on observing the surface community formed by bacteria during 24-hour contact. The results of microbial barrier tests and biofilm tests should be reported separately and distinguished from the main indicator of viable bacteria number changes.

5.3. Cell Compatibility at the Measured Release Exposure

Frankova et al. observed the responses of human fibroblasts and keratinocytes to AgNPs for 24 and 48 hours, and found that the levels of various inflammatory-related

substances and VEGF decreased, with keratinocytes being more sensitive [21]. Galandakova et al.'s research showed that under similar experimental conditions, silver ions were more toxic to cells than silver nanoparticles [22]. These results indicate that the safety assessment of silver-containing hydrogels needs to focus on the impact of silver release on cellular inflammatory responses and tissue repair. Currently, there are differences in the performance of different silver-containing dressings in cells and tissues [23-25], and the appropriate range of silver exposure for hydrogels still needs further research. Therefore, in addition to measuring the amount of silver release, the antibacterial effect and cell compatibility of the material should also be evaluated.

ISO 10993-5 provides a basis for in vitro cytotoxicity testing, and ISO 10993-12:2021 (revised in 2025) and ISO 10993-18:2020 (revised in 2022) respectively involve sample preparation and chemical composition analysis [44-46]. It is recommended to test the silver-free hydrogel first to understand the impact of polymer materials and their release products on cells, and then add AgNP for comparison. For silver-containing materials, the additional effects produced by adding silver should be determined in combination with the amount of silver release and the silver-free hydrogel control. After the preliminary cell test is completed, a more comprehensive biosafety evaluation should be carried out to clarify the individual effects of polymers and silver nanoparticles and ensure that the candidate material has basic cell compatibility.

Cell compatibility is evaluated by the number of surviving cells after 24 hours of contact with the material, including normal human dermal fibroblasts and keratinocytes, and compared with untreated cells. At the same time, the integrity of the cell membrane should be observed to more comprehensively judge the cell state. Cell morphology and metabolic activity can be used as auxiliary indicators. After the initial test, further evaluation of the material's impact on wound repair-related cells should be conducted. Due to the possible differences in the response of different cells to silver, both types of cells should reach the preset standards to support the judgment that the material has good cell compatibility.

Silver nanoparticles may affect colorimetric and fluorescence detection, causing deviations in the measurement results [47]. Therefore, the results should be verified by another detection method during the test. After confirming the reliability of the data, the material's compliance with DR3 requirements should be judged based on the cell test results, avoiding regarding the test error as cell damage or activity changes.

5.4. Defining the Acceptable Biological Range

The release amount of silver needs to reach the antibacterial target while ensuring that both types of cells can maintain their normal state and that the material properties remain stable. During the assessment, the actual exposure amount of silver should be compared with the antibacterial effect and the cell response under the same experimental conditions. The addition amount of AgNP in the formula also needs to be recorded separately because it is not the same as the amount of silver released into the surrounding environment. Finally, only the exposure range that meets both antibacterial and cell safety requirements can be considered as acceptable.

Before the formal test, the candidate exposure range, qualification standards, and re-testing rules should be clearly defined, including the number of repetitions required for the same batch to be tested, and how to handle unclear results (Section 6). Only when both antibacterial and cell tests meet the preset standards can the exposure condition be judged as qualified. If a confidence interval is used for judgment, the interval must also be completely within the qualified range. If the results clearly exceed any standard, it indicates unqualified. If the results are still within the critical range, a re-test should be conducted according to the pre-determined plan. For cases where abnormal detection or differences in repeated results exist, the cause should be identified first before making a judgment. The applicable range finally confirmed should be based on the actual test results and distinguish between clearly unqualified, results still uncertain, and detection invalid situations, so as to determine the subsequent research direction.

Materials evaluated by DR3 can enter DR4 to continue examining the effects of processing and storage aging on the materials. If all preset conditions clearly fail to meet at least one requirement, the silver-containing scheme should be terminated. If there are still uncertainties in the test results, a limited number of re-tests should be conducted according to the pre-determined plan. The plan should clearly state the reasons for re-testing, the upper limit of the number of additional tests, and how to comprehensively judge all valid results. Throughout the process, the original qualification standards should be maintained to avoid the influence of repeated tests on the judgment. If a clear conclusion cannot be reached after re-examination, the current silver-containing solution should be terminated due to insufficient evidence, and the identified biological safety issues should be recorded separately.

When using an anti-bacterial formula without silver, AgNP should be removed and the antibacterial performance statement should be adjusted. At the same time, the basic performance, cell compatibility, and the effects of processing and aging of the hydrogel should be re-evaluated. After adopting the new silver-containing formula, a revalidation is necessary. DR3 mainly examines the biological safety of the silver-containing formula, while DR5 focuses on whether the hydrogel system can provide sufficient protection for the tissue. Regardless of the stage of the research and development, as long as the material fails to meet the requirements of DR5, the entire plan should be halted.

6. Decision Framework and Validation Sequence

This study assesses the materials, dressings, and their application methods as a whole. Figure 1 illustrates the clinical usage requirements, material performance, and their impact on the wound tissue that need to be considered in the assessment. Table 3 lists the criteria for determining whether a product is suitable for further development, as well as situations where modifications or discontinuation of development are required.

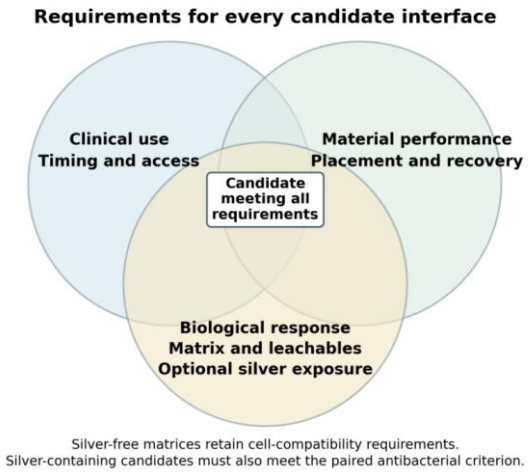


Figure 1. Clinical-use, Material-Performance, and Biological-Response Requirements. All Candidates Require Matrix Compatibility; Silver-Containing Candidates Additionally Require Paired Antimicrobial and Cell-Response Acceptance.

Before formal testing, available evidence, the performance of existing dressings, and clinical requirements should be considered when establishing acceptance criteria and accounting for measurement errors. Subsequent tests will be judged according to these standards. If the assessment reveals that the material may seriously damage the wound tissue, the current plan should be immediately terminated. The residue of the material and the release of silver also need to meet the requirements specified in Table 3. If the product design is adjusted, relevant performance tests need to be conducted again.

Table 3 explains the problems that need to be solved at each stage. The focus of each stage of the assessment is different. DR1 compares the new system with the existing

dressings to determine if its effectiveness has improved. DR2 focuses on whether the material can be removed smoothly, and DR3 examines whether the silver formula is safe. After entering DR4, it is also necessary to evaluate whether the processing and storage have changed the performance of the material or the release of silver. DR5 focuses on whether the material can properly protect the wound tissue when used.

DR1 measures the proportion of the area where the dressing remains in contact with the simulated wound 24 hours after application to determine its fitting effect. Gel dressings and control dressings need to be tested under the same conditions and the actual contact area and the gap between the dressing and the wound should be observed through imaging. During measurement, the original fitting state of the dressing should be maintained to avoid the influence of the operation on the results.

The contact coverage rate is used to determine whether the dressing can maintain a good fit with the wound. The minimum passing standard should be determined based on preliminary tests and clinical evaluations, taking into account measurement errors. An increase in the contact area does not necessarily indicate better results. If this causes fluid accumulation or affects wound inspection, it cannot be regarded as an improvement in performance. Before the formal tests, the arrangement for repeated tests and the method for result determination need to be determined. If the test results are still not clear and cannot prove that the dressing has improved, the process should be postponed. Subsequent evaluations will be carried out according to the pre-determined plan. DR2 mainly checks whether there is any material residue after the dressing is removed, and DR5 focuses on whether the markings required for subsequent inspections are clearly visible.

The entire verification process starts from the actual clinical needs. Surgeons, nurses, and transport personnel first jointly review the problems existing in the conventional dressings in wound care and select an appropriate control group (Section 2.3). Subsequently, researchers would first test the base formula without silver to observe its performance during application and removal, and assess its effects on cells (Sections 4.3 and 5.3). The evaluated formula can then enter the comparison of the complete dressing system. If silver nanoparticles are to be added to the formula, additional verification is required to confirm the release of silver and its impact on cells, and the specific process is shown in Figure 2.

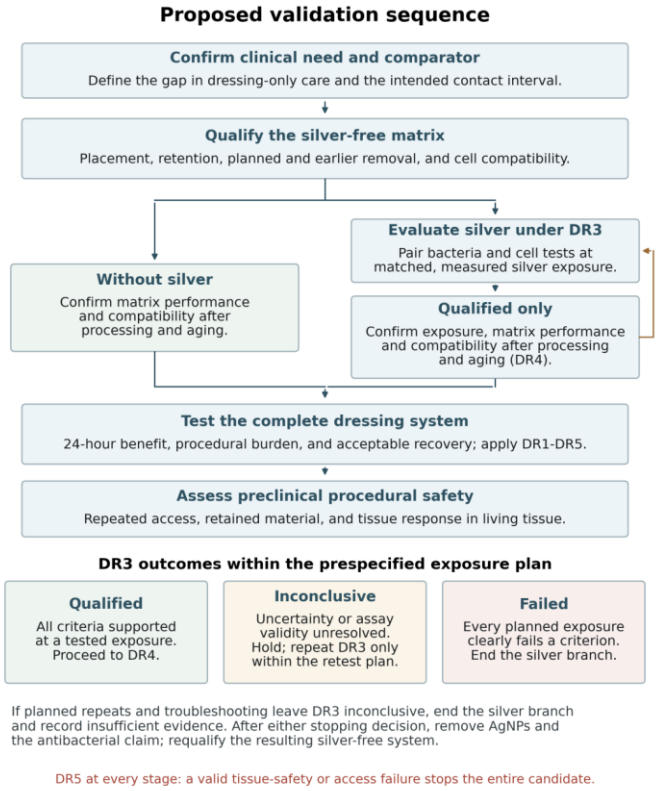


Figure 2. Proposed Validation Sequence and DR3 Outcomes. Qualified Exposures Proceed to DR4; Inconclusive Results Follow Bounded Retesting, and Failed or Unresolved Branches End as Defined in Section 5.4. The Return Arrow Denotes Repeat Qualification After Processing or Aging Changes. Both Routes Retain Matrix Requirements, and DR5 Takes Precedence Throughout.

For silver-containing formulas, it is also necessary to check whether the particle state changes after the addition of silver nanoparticles. Then, through testing, it is determined whether the material can inhibit bacteria while maintaining an acceptable cell response to determine whether it passes the DR3 assessment (Section 5.4; Figure 2). The evaluated formula will then enter DR4 to further check whether production, sterilization, and storage aging affect the material performance. If the release of silver changes, it needs to be re-tested according to the predetermined process and record the changes in test conditions. All candidate materials, regardless of whether they contain silver, should be subjected to biological safety assessment in accordance with ISO 10993-1 standard [48].

The 24-hour comprehensive test is used to observe whether the materials can maintain good performance under conditions close to those of actual use after being fully incorporated into the dressing system. During the test, the hydrogel dressings and conventional dressings should be compared in the same wound model and bacterial environment, and the possible shaking during transportation should be simulated (Sections 2 to 5; Table 1). The focus of the assessment is the degree of adhesion of the dressings to the wound 24 hours after application, and whether leakage or displacement occurs to determine whether the adhesion effect can be an advantage in actual use. Whether the medical staff can easily apply and remove the materials, and whether the wound can be smoothly inspected after removal, will also affect the final judgment.

Only when the materials meet the performance requirements and the operation process is in line with expectations can further animal experiments be conducted to evaluate their performance in contaminated deep soft tissue injuries. Such experiments can observe the effect of the materials when repeatedly contacting living tissue, especially to confirm whether removing the materials will damage the tissue and whether the residues will hinder subsequent debridement. For silver-containing materials, local tissue examination and systemic silver exposure should also be evaluated.

7. Discussion and Limitations

This framework assesses whether candidate products are worth further development from three aspects: the material itself, antibacterial effect, and actual use. If the performance of the basic hydrogel and cell safety meet the requirements, an unsilvered formula can be considered. After adding silver nanoparticles, it is necessary to confirm that the release amount of silver is within an acceptable range and understand whether processing and storage will change this release situation. If the silver-containing scheme is stopped due to safety risks or insufficient existing evidence, the basic hydrogel may still continue to be developed, but after switching to an unsilvered formula, the entire dressing system still needs to be re-tested. Antibacterial efficacy is only part of the evaluation of the dressing. The dressing should also be easy to remove so that healthcare workers can smoothly inspect and clean the wound. By comprehensively considering these aspects, it will be possible to clearly identify the issues that still need to be addressed in the subsequent development.

Clinical needs determine the applicable scenarios of this framework. Existing trauma studies mostly adopt observational designs, and the research results are closely related to specific debridement methods and clinical practices. Case studies of NPWT and aviation medical reports indicate that this method has application value under certain conditions [8-12]. Trials on rinsing and NPWT for open fractures provide other references for relevant clinical decisions [49,50]. The proposed hydrogel interface in this study mainly targets situations where conventional dressings can still meet basic nursing needs, but have obvious limitations in actual use. At this time, adding the hydrogel interface is expected to improve wound care. Practical application also requires combining wound debridement arrangements, equipment conditions, staff configuration, wound status, and the nursing capabilities of the receiving institution to determine the applicability of the scheme.

Existing research provides the material and technical basis for this scheme. The OAlg-CMCS polymer research mainly involves cell delivery and wound repair [13-17], while other hydrogel studies have adopted different material compositions [18-20]. Table 2 summarizes the dissolution studies, providing a reference for the removal design of hydrogels in burn care [34,35]. The OAlg-CMCS formula proposed in this study and its removal effect from the wound gap in the trauma wound area still need to be verified through specialized tests. The performance of AgNP is closely related to particle characteristics, storage aging, surrounding medium, and detection methods [21-29], and the research results on human lung cells [30] also provide a reference for the selection of subsequent wound-related models. Existing literature is mainly used to integrate design basis. Further research needs to expand the range of material comparisons and combine clinical opinions and preliminary trials to clarify the main efficacy indicators, removal process, and qualification standards. When applying this framework to other materials, assessment requirements should also be adjusted according to specific purposes.

8. Conclusion

The temporary hydrogels for staged trauma amputation care should be evaluated as a whole, considering materials, outer dressings, and removal methods. The proposed framework uses conventional dressings as a comparator, specifies how the potential benefits of the hydrogel should be evaluated, and incorporates tissue protection and subsequent wound examination into the assessment. All candidate materials need to pass basic performance and biological safety tests. The silver-containing formula also needs to prove that it can effectively inhibit bacteria under the predetermined usage conditions while maintaining an acceptable cell response. Researchers can decide to continue development, adjust the formula, or terminate the scheme based on pre-set standards. The next step is to verify the removal effect and overall performance of the materials in the target wound environment to provide a basis for subsequent clinical application.

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Data Availability Statement: No new experimental data were generated. The targeted literature-search methods and selection record are provided in Appendix A.

Institutional Review Board Statement: Not applicable. This article evaluates published literature and does not report new studies involving human participants or animals.

Author Contributions: Shunkai Zhu conceived the article, selected and evaluated the relevant literature, developed the comparative framework, interpreted the evidence, and reviewed and approved the final manuscript.

Use of Generative Artificial Intelligence: OpenAI's ChatGPT was used to assist with drafting and revising text, organizing the manuscript, developing candidate comparison frameworks and evaluation criteria, preparing schematic figures, supporting targeted literature searches and screening, and checking selected references. The author is responsible for verifying the cited sources, evaluating the scientific interpretations, and approving the manuscript submitted for publication, and takes full responsibility for its content.

Appendix A. Supplementary Search Record

A Decision Framework for Removable Hydrogel Interfaces in Traumatic Amputation Care

Search performed on 11 September 2026

A.1. Scope

This record documents a targeted literature check performed for the present revision. It supplements the references already assembled during framework development. It does not reconstruct the original retrieval of every clinical guideline, material paper, or assay standard, and it is not a systematic review protocol or a claim of exhaustive coverage.

A.2. Database and Execution

Database: PubMed. Interface: NCBI E-utilities (ESearch and EFetch). Search fields: title and abstract. Publication-date range: 1 January 1800 to 11 September 2026, with the lower date used as a broad database bound. No language, species, study-type, or full-text-availability filter was applied. Results were returned in relevance order; all returned records were retrieved.

A.3. Search 1 for the Illustrative Polymer Pair

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hydrogel*[Title/Abstract] AND ("oxidized alginate"[Title/Abstract] OR "alginate
dialdehyde"[Title/Abstract]) AND ("carboxymethyl chitosan"[Title/Abstract] OR
carboxymethylchitosan[Title/Abstract])
```

Returned records: 24. Date filter applied separately through the publication-date field (pdat).

A.4. Search 2 for Removable Interfaces

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hydrogel*[Title/Abstract] AND (wound*[Title/Abstract] OR burn*[Title/Abstract] OR
dressing*[Title/Abstract]) AND (removab*[Title/Abstract] OR dissolvab*[Title/Abstract] OR "on
demand"[Title/Abstract] OR "on-demand"[Title/Abstract] OR "triggered
dissolution"[Title/Abstract])
```

Returned records: 410. Date filter applied separately through the publication-date field (pdat).

The two result sets contained 24 and 410 records, respectively, with no PMID overlap (434 unique records). These are retrieval counts, not numbers of studies included in an evidence synthesis. The asterisk is the PubMed truncation operator. The removal query intentionally did not restrict polymer chemistry or require the word amputation.

A.5. Selection and Access

All 434 titles were reviewed. Twelve representative records from the removal search were selected for closer abstract reading to examine distinct triggers, chemical proximity, and model relevance; the selection is documented below. Cook et al. was also checked

against its publicly accessible full text. The other eleven entries were considered at abstract level. Quantitative claims requiring unavailable full text were not added to the manuscript.

The direct removal comparison prioritized original reports that specified how the interface was dismantled or detached. Network dissolution, detachment, and tissue clearance were treated as different endpoints; wound healing alone was not taken as proof of complete removal. Reports centered only on stimulus-controlled payload release, dissolving delivery devices, or unrelated tissue applications were not selected as direct dressing-removal evidence. An Account was considered as context, without counting it as an additional independent experiment.

Previously identified Huang and Cook records were retrieved again and retained for CMCS chemistry and porcine burn evaluation, respectively. Alternative triggers were considered without ranking clinical performance.

A.6. Representative Appraisal Record

The entries in Table A1 document the bounded selection, not all potentially relevant papers in the 410-record search. Except for Cook, mechanism descriptions are limited to the indexed abstracts. The final column states the use made of the record in this revision.

Table A1. Representative appraisal records documenting the bounded selection.

Record and access link	Removal mechanism reported	Use and selection rationale
Huang 2018 CMCS and DACNC PMID 30398062	Amino acid solution dissolves a dynamic Schiff-base network.	Retained in Section 4.1 and Table 2 for chemical proximity. Abstract only; no concentration or dissolution-time detail was imported.
Cook 2021 PEI and PEG PMID 34486599	Cysteine methyl ester cleaves thioester-containing crosslinkers.	Retained for explicit removal and porcine burn evaluation. Full text checked; rheological dissolution was distinguished from tissue clearance.
Diselenide-containing hydrogel PMID 32658477	Oxidation or reduction disrupts diselenide crosslinks.	Alternative redox-triggered chemistry considered. Not used as evidence for recovery from an amputation wound.
Physical chitosan hydrogel PMID 35868791	Dilute acetic acid enables dissolution.	Alternative pH-dependent route considered. Pure chitosan differs from the proposed CMCS network.
Trigger-detachable adhesive hydrogel PMID 35460194	Shear disrupts noncovalent supramolecular interactions.	Considered as detachment rather than chemical dissolution. Peeling and tissue-clearance endpoints must remain distinct.
Dissolvable PEG hemostatic sealant PMID 35436591	An exogenous thiolate solution induces thiol-thioester exchange.	Considered for removal after hemorrhage control. Its emergency hemostasis role differs from the post-debridement interface defined here.
Supramolecular hybrid burn dressing PMID 37056249	Amantadine hydrochloride disrupts host-guest interactions.	Alternative supramolecular route considered. Abstract-level biocompatibility observations were not treated as amputation or burn-healing efficacy.

Calcium alginate and carbon dots PMID 39095807	Carbon-dot-assisted mineralization removes calcium crosslinks.	Alternative ionic-network route considered. Calcium alginate dissolution does not establish dissolution of an imine-crosslinked OAlg-CMCS matrix.
Photolabile PEG and glycol chitosan PMID 31475280	UVA cleaves photocleavable crosslinks.	Alternative light-triggered route considered at abstract level. Linked correction PMID 33660734 was identified; see access note below.
PEG thiols and oxidized dextran PMID 33448806	Free thiols shift thiol-hemithioacetal exchange and dissolve the network.	Alternative dynamic-covalent route considered. Polymer chemistry differs; no direct clearance claim was transferred.
DNA-crosslinked mucin hydrogel PMID 38217373	Temperature changes or DNA displacement strands cause gel-to-sol transition.	Mechanistic context only. The abstract proposes wound applications without demonstrating wound-dressing removal in a wound model.
Account on dissolvable chemical networks PMID 28170219	Discusses thiol-thioester and other reversible crosslinking approaches.	Context only. Not counted as a new primary experiment or added as independent efficacy evidence.

A.7. Access and Interpretation Limits

The linked correction to the photolabile study was checked (PMID 33660734; https://doi.org/10.1039/D1TB90031E). It adds an omitted author affiliation and does not revise the material results. The original study was considered only as an abstract-level alternative, with no quantitative result transferred to the manuscript. Huang remains abstract-supported pending author full-text verification. The other alternative entries are leads and mechanistic context, not fully appraised substitutes for the proposed candidate.

This single-database, purposive check can miss records because of indexing, terminology, language of appraisal, and source access. No independent duplicate screening, formal risk-of-bias assessment, certainty grading, or meta-analysis was performed. Failure to select a record for the compact evidence table does not imply that its chemistry is ineffective or unsafe. The search record supports transparency about the revision; it does not establish completeness or clinical validity.

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