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Review Article

Antibiotic Resistance and Antibiotic-Loaded Hydrogel Formulations: A Review

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ABSTRACT

Antimicrobial resistance (AMR) has reduced the reliability of conventional antibiotic therapy and is particularly challenging in localized infections, where systemic administration may produce inadequate concentrations at the infected site while increasing systemic exposure. Hydrogels are three-dimensional hydrated polymeric networks that can serve as local drug reservoirs, conform to irregular tissue surfaces, retain wound fluid, and modulate antibiotic release. This review examines the relationship between AMR and localized infection, the physicochemical characteristics and classification of hydrogels, fabrication approaches, representative antibiotic-loaded hydrogel systems, formulation and evaluation strategies, and combination approaches intended to improve antibacterial activity or address biofilm-associated tolerance. Evidence from aminoglycoside-, fluoroquinolone-, glycopeptide-, beta-lactam-, and other antibiotic-containing systems demonstrates that polymer selection, cross-linking density, porosity, drug-polymer interactions, and the intended anatomical site strongly influence release and biological performance. Recent studies also illustrate the use of chitosan, gellan gum, silk-based hydrogels, dendrimer networks, and metal-containing composites for localized antimicrobial delivery. Particular attention is given to antibacterial activity, swelling, rheology, morphology, drug release, release kinetics, cytocompatibility, and in vivo wound models. Combination systems involving more than one antibiotic, antimicrobial enzymes, or inorganic antimicrobial components may broaden antibacterial mechanisms, but their benefits must be established using appropriate synergy and translational models. The review concludes that antibiotic-loaded hydrogels are a versatile local-delivery platform, while reproducible manufacturing, sterilization, stability, dose optimization, regulatory characterization, and clinically relevant efficacy studies remain important barriers to wider clinical translation.

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1. INTRODUCTION

Antibiotics transformed the management of bacterial infection and enabled major advances in surgery, transplantation, cancer treatment, intensive care, and other areas of medicine. Their effectiveness, however, is increasingly challenged by antimicrobial resistance, in which microorganisms acquire or express mechanisms that reduce susceptibility to antimicrobial agents. The global burden is substantial. The Global Burden of Disease analysis for 1990–2021 estimated 4.71 million deaths associated with bacterial AMR in 2021, including 1.14 million deaths attributable to bacterial resistance.¹ The World Health Organization's 2024 bacterial priority pathogens list further emphasizes the need for new antibacterial approaches against organisms for which therapeutic options are increasingly constrained.²

The problem is not limited to systemic infection. Wounds, burns, ocular infections, periodontal infections, and implant-associated infections may contain necrotic tissue, extracellular polymeric matrices, impaired vascular supply, or heterogeneous microbial populations. These features can complicate antibiotic penetration and produce local conditions in which bacteria survive despite antibiotic exposure. Biofilms are particularly important because the matrix, altered metabolic state, and physiological heterogeneity of biofilm communities can reduce antimicrobial susceptibility.³

Localized delivery therefore represents a complementary strategy rather than a replacement for appropriate systemic treatment. A local carrier can concentrate an antimicrobial at the target site, prolong residence time, reduce the frequency of administration, and potentially reduce systemic exposure. Hydrogels are attractive in this context because their high water content and tunable

polymer networks permit incorporation of hydrophilic drugs and biological agents while providing a conformable material that can be applied to irregular surfaces.^{4–6}

This review focuses on antibiotic-loaded hydrogels in the context of AMR and localized infection. It synthesizes the principles governing hydrogel design, summarizes representative antibiotic-loaded systems, compares evaluation methods, and discusses combination strategies and translational challenges. The emphasis is on formulation–performance relationships rather than on any single antibiotic or polymer.

2. THE GLOBAL ANTIMICROBIAL RESISTANCE CRISIS

2.1 Epidemiology and burden

Bacterial AMR is a global public-health problem with substantial mortality and morbidity. The 2024 Global Burden of Disease analysis estimated 4.71 million deaths associated with bacterial AMR in 2021 and 1.14 million directly attributable deaths.¹ These estimates demonstrate the scale of the problem while also illustrating why local and systemic antimicrobial strategies need to be considered together. The WHO bacterial priority pathogens list categorizes organisms according to public-health importance and research and development needs, with resistant Gram-negative pathogens and resistant Gram-positive organisms among major priorities.²

The epidemiology of AMR is heterogeneous across regions, age groups, organisms, and infection sites. Differences in antibiotic consumption, infection-control practices, diagnostic capacity, access to effective treatment, vaccination, sanitation, and healthcare infrastructure all contribute to the observed burden. Consequently, a delivery platform should



not be viewed as an isolated solution to AMR. Instead, hydrogel-based local delivery may be most useful when combined with microbiological diagnosis, antimicrobial stewardship, infection prevention, and appropriate systemic or surgical management.

2.2 Mechanisms of antibiotic resistance

Bacteria can resist antibiotics through several broad mechanisms. These include enzymatic drug inactivation, modification or protection of the antibiotic target, reduced permeability or uptake, and active efflux.³ Enzymatic inactivation is exemplified by beta-lactamases and aminoglycoside-modifying enzymes. Target modification may involve altered penicillin-binding proteins, ribosomal changes, or mutations affecting antibiotic binding. Reduced permeability can result from changes in membrane proteins or porins, while efflux pumps can actively export antimicrobial molecules from the bacterial cell.

Biofilm-associated tolerance adds another layer of complexity. Biofilm cells may experience reduced growth rates, altered metabolic states, restricted diffusion through extracellular polymeric substances, and phenotypic heterogeneity.³ These features do not necessarily represent heritable resistance in the classical sense, but they can produce clinically important reductions in antimicrobial effectiveness. For local infections, the formulation must therefore be evaluated not only for planktonic antibacterial activity but, where relevant, for activity against biofilms or other clinically representative models.

2.3 Localized infection as a distinct delivery problem

In a localized infection, the therapeutic objective is to expose the infected tissue to an effective concentration for an adequate period while

minimizing unnecessary systemic exposure. Conventional oral or parenteral therapy may be limited by distribution, tissue perfusion, binding, metabolism, clearance, and dose-related toxicity. Aminoglycosides illustrate the issue because systemic exposure can be associated with nephrotoxicity and ototoxicity, whereas a topical or localized formulation can place the drug closer to the target site.

A hydrogel can function as a reservoir from which the antibiotic is released by diffusion, polymer relaxation, swelling, degradation, or combinations of these processes. The release mechanism is influenced by mesh size, cross-link density, polymer charge, drug molecular size, drug–polymer interactions, and environmental conditions.^{4,5} Therefore, hydrogel development requires simultaneous consideration of microbiological activity, drug stability, polymer chemistry, and intended clinical use.

3. HYDROGELS AS DRUG DELIVERY SYSTEMS

3.1 Definition and general properties

Hydrogels are three-dimensional networks of hydrophilic polymers capable of absorbing and retaining large quantities of water while maintaining a defined network structure.^{4,5} Their hydrated environment can support diffusion of water-soluble molecules and provides a soft, tissue-compatible material for topical or injectable applications. Important properties include swelling capacity, water retention, mechanical strength, viscoelasticity, porosity, biodegradability, surface characteristics, and release behavior.

For wound applications, water retention and exudate handling can be beneficial because an appropriately hydrated environment can protect



the wound surface and facilitate controlled drug delivery. At the same time, excessive swelling or inadequate mechanical strength may cause poor handling or loss of structural integrity. Thus, an optimal formulation balances hydration with mechanical stability.

3.2 Classification of hydrogels

Hydrogels may be classified according to polymer source, cross-linking mechanism, network architecture, or responsiveness. Natural polymers include chitosan, alginate, gelatin, hyaluronic acid, and dextran. Synthetic systems include poly(vinyl alcohol), poly(ethylene glycol) derivatives, polyacrylamide, and related materials. Hybrid hydrogels combine natural and synthetic components to integrate biological functionality with mechanical control.^{6–9}

Cross-linking may be physical or chemical. Physical networks are formed through ionic interactions, hydrogen bonding, hydrophobic association, crystallization, or other reversible interactions. Chemical networks involve covalent bonds and may provide greater resistance to dissolution. The choice of cross-linking strategy influences swelling, degradation, mechanical strength, drug diffusion, and potential cytotoxicity of residual cross-linkers.

Stimuli-responsive hydrogels are designed to alter swelling, network structure, or drug release in response to environmental conditions such as pH, temperature, ionic strength, enzymes, or reactive species. Recent chitosan/PVP/PEG systems cross-linked with tetraethyl orthosilicate illustrate how network chemistry can be used to obtain pH-dependent release and antimicrobial performance.¹⁰

3.3 Fabrication techniques

Common fabrication approaches include solution casting, ionic gelation, covalent cross-linking, freeze–thaw processing, electrospinning, photocrosslinking, and additive manufacturing. Freeze–thaw cycles are widely used to produce physically cross-linked poly(vinyl alcohol) networks without conventional chemical cross-linkers. Ionic gelation is especially relevant to chitosan because its protonated amino groups can interact with multivalent anions such as tripolyphosphate. Chemical cross-linking can provide additional network stability but requires careful evaluation of residual reagents and biological compatibility.

Injectable and in situ-forming hydrogels provide an alternative for irregular wounds, periodontal pockets, and ocular surfaces. Photocurable silk-based hydrogels, for example, can be formed rapidly in situ and have been investigated for corneal repair while delivering gentamicin locally.¹¹ Additive manufacturing and 3D printing can further provide control over geometry and porosity, although the compatibility of printing conditions with antibiotic stability must be established.

4. ANTIBIOTIC-LOADED HYDROGEL FORMULATIONS: REPRESENTATIVE SYSTEMS

4.1 Aminoglycoside-loaded hydrogels

Aminoglycosides are attractive candidates for localized hydrogel delivery because many are water soluble and have established antibacterial activity. Gentamicin-loaded chitosan-based hydrogel films have been developed for antibacterial wound dressings. Zhang et al. prepared cross-linked chitosan quaternary ammonium salt hydrogel films containing gentamicin sulfate and characterized their physicochemical and antibacterial properties.¹²



Such systems illustrate the potential to combine the intrinsic antibacterial characteristics of a cationic polymer with antibiotic activity.

A more recent framycetin sulphate hydrogel dressing used poly(vinyl alcohol), sodium alginate, and polyvinylpyrrolidone with freeze-thaw processing. The formulation showed swelling, sustained drug release, SEM and FTIR characterization, and improved wound healing in an animal model.¹³ These studies emphasize that the value of an antibiotic-loaded hydrogel is determined by the complete formulation profile rather than by drug loading alone.

Gentamicin has also been incorporated into photocurable methacrylated silk hydrogels for corneal repair. The hydrogel could be formed rapidly using low-intensity UV exposure and inhibited *Staphylococcus aureus* and *Pseudomonas aeruginosa* growth for up to 72 h *in vitro*.¹¹ The example demonstrates how the same antibiotic can be adapted to a different anatomical site by changing the polymer network and application method.

4.2 Fluoroquinolone-loaded hydrogels

Fluoroquinolones have been incorporated into polymer networks to provide local sustained delivery. Recent work on chitosan/PVP/PEG networks cross-linked with tetraethyl orthosilicate examined ciprofloxacin-containing formulations and demonstrated pH-dependent swelling and drug release together with antimicrobial activity.¹⁰ Such systems are relevant to localized infections because environmental responsiveness may permit release to be modulated by the physicochemical conditions surrounding the formulation.

When evaluating fluoroquinolone hydrogels, attention should be given to drug stability, polymer interactions, burst release, cumulative release, and

maintenance of antibacterial activity after incorporation. A high initial release may provide rapid antimicrobial action but shorten the duration of local exposure, whereas an overly restrictive network may reduce the concentration available at the infection site.

4.3 Glycopeptide-loaded and dual-antibiotic hydrogels

Gellan gum has been investigated as a matrix for topical delivery of vancomycin and clindamycin in infected diabetic wounds. A spongy gellan-gum hydrogel provided controlled release of both antibiotics and showed antibacterial activity against MRSA, with the therapeutic concept evaluated further in a diabetic mouse wound model.¹⁴ The study illustrates a clinically relevant principle: local combination therapy can be designed to maintain antibacterial exposure while reducing the limitations of repeated systemic administration.

Gellan-gum systems can also be engineered with particulate components to modify drug release. Earlier work on tunable antibacterial gellan hydrogels investigated vancomycin and activated carbon as components of a controlled-release system for burn-wound applications.¹⁵ Such approaches show how the carrier can be treated as an active design variable rather than simply an inert vehicle.

4.4 Beta-lactam-loaded dendrimer hydrogels

Dendrimer hydrogels represent a distinct class of highly functionalized polymer networks. A recent study developed polyamidoamine G5 dendrimer/PEG-diacrylate hydrogels containing cefazolin for local delivery associated with periodontal bone regeneration.¹⁶ *In vitro* release testing over 72 h demonstrated slower release from the hydrogel than from control samples without



hydrogel. This example highlights the importance of electrostatic interactions and network entrapment in controlling release of a hydrophilic antibiotic.

4.5 Other antibiotic classes and emerging systems

The range of antibiotics compatible with hydrogel delivery continues to expand. In addition to aminoglycosides, fluoroquinolones, glycopeptides, and beta-lactams, tetracyclines and other antimicrobial agents can be incorporated into polymeric networks or composite scaffolds. Recent 3D-printed antibiotic-releasing constructs

demonstrate how controlled porosity and scaffold architecture can be integrated with antimicrobial delivery for tissue engineering applications.¹⁷

The comparative literature suggests that no single hydrogel architecture is universally optimal. Natural polymers may provide biological functionality and biodegradability, synthetic polymers can offer greater control over mechanical properties and network structure, and composite systems can combine multiple functions. The appropriate design depends on the antibiotic, target microorganism, anatomical site, required duration of therapy, mechanical demands, and intended route of administration.

Table 1. Representative antibiotic-loaded hydrogel systems

Hydrogel system	Antibiotic/agent	Target application	Reported function	Key formulation feature
Chitosan-based hydrogel	Gentamicin	Wound dressing	Antibacterial activity; controlled local delivery	Natural cationic polymer; tunable cross-linking
PVA/PVP/alginate hydrogel	Framycetin sulphate	Wound healing	Swelling and sustained release; in vivo wound healing	Freeze-thaw physical network
Methacrylated silk hydrogel	Gentamicin	Corneal repair	72 h inhibition of <i>S. aureus</i> and <i>P. aeruginosa</i>	Photocurable, conformable network
Chitosan/PVP/PEG hydrogel	Ciprofloxacin	Localized antimicrobial delivery	pH-responsive swelling and release	TEOS cross-linking
Gellan-gum hydrogel	Vancomycin + clindamycin	MRSA-infected diabetic wound	Controlled dual-antibiotic release; in vivo efficacy	Spongy hydrogel architecture
PAMAM/PEG-diacrylate hydrogel	Cefazolin	Periodontal bone regeneration	Sustained in vitro release	Dendrimer-based network
Metal/nanoparticle hydrogel composites	Various antibiotics/antimicrobials	Wound and surface infection	Multi-mechanistic antimicrobial activity	Composite inorganic/polymer system



5. FORMULATION APPROACHES AND EVALUATION PARAMETERS

Hydrogel development should proceed through a rational sequence: selection of the polymer and cross-linking strategy; assessment of drug–polymer compatibility; optimization of polymer concentration, cross-link density and drug loading; and evaluation of physicochemical, mechanical, release, microbiological and biological performance. The same formulation may behave differently when transferred from a small laboratory sample to a larger batch, making reproducibility an important consideration.

5.1 Preformulation and compatibility

Drug–excipient compatibility can be investigated using FTIR spectroscopy, differential scanning calorimetry, thermogravimetric analysis, microscopy, and complementary techniques. FTIR can identify changes in characteristic functional-group bands, while thermal analysis can reveal changes in melting, decomposition, or interaction behavior. These methods should be interpreted together rather than as definitive proof of compatibility on the basis of a single spectral shift.

5.2 Physical and physicochemical characterization

Appearance, homogeneity, pH, gelation time, swelling, water retention, and stability are fundamental measurements. The pH should be appropriate for the intended application and should not adversely affect drug stability or tissue compatibility. Swelling ratio provides information about the amount of fluid that the network can absorb and is related to mesh size and cross-link density. Excessive swelling may weaken a dressing, whereas insufficient swelling may limit exudate handling and drug mobility.

5.3 Rheological and mechanical evaluation

Rheology is particularly important for semisolid, injectable, and wound-dressing hydrogels. Viscosity as a function of shear rate, storage modulus, loss modulus, yield stress, and recovery after deformation can provide information about handling and structural recovery. Recent work on PVA/chitosan/gentamicin hydrogels demonstrates that incorporation of chitosan and antibiotic can measurably alter viscoelastic behavior, illustrating the need to characterize the final drug-loaded formulation rather than extrapolate from the blank polymer network.¹⁸

5.4 Morphology and network structure

SEM is commonly used to visualize pore architecture after appropriate sample preparation. Pore size, pore interconnectivity, and surface morphology influence fluid uptake and drug diffusion. However, drying can alter the native hydrated structure of a hydrogel; therefore, SEM findings should be interpreted as morphological evidence rather than a direct representation of the intact hydrated network. Other methods, including cryo-SEM or microscopy of hydrated specimens, may provide complementary information when available.

5.5 Entrapment efficiency and drug loading

Drug loading and entrapment efficiency quantify how much active ingredient is incorporated relative to the amount used during preparation. These parameters should be reported with the analytical method, calibration range, recovery, sample preparation, and replicate information. For protein or enzyme components, activity should be assessed in addition to concentration because an apparently high loading value does not establish preservation of biological function.



5.6 In vitro drug-release studies

Drug release may be evaluated using dialysis membranes, diffusion cells, dissolution systems, or other validated setups depending on the formulation and intended route. The experimental medium, temperature, membrane characteristics, sampling schedule, replacement volume, and analytical method should be described clearly. UV–visible spectrophotometry may be suitable when the drug has adequate selectivity and sensitivity, whereas HPLC may be preferable when matrix interference or multiple analytes are present.

Release data can be fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models when appropriate. The Korsmeyer–Peppas equation is useful for describing release behavior from polymeric systems, but model fitting should not be interpreted as definitive mechanistic proof without considering the underlying formulation and experimental design.¹⁹

Antibacterial testing may include agar diffusion, broth microdilution, minimum inhibitory concentration, minimum bactericidal concentration, and time-kill methods. Diffusion-based assays are useful for screening but are strongly influenced by the ability of the antibiotic to diffuse from the hydrogel. Therefore, a small inhibition zone does not necessarily indicate poor antibacterial activity if the drug has limited diffusion through agar. For combination systems, checkerboard microdilution can be used to calculate the fractional inhibitory concentration index, while time-kill testing can provide dynamic information about bactericidal interactions.²⁰

Where biofilm infection is central to the intended application, biofilm biomass, viable cell counts, metabolic activity, microscopy, or other validated endpoints should be selected according to the study question. Because biofilm models differ substantially in organism, surface, medium, maturation time, and endpoint, comparisons across studies should be made cautiously.

5.7 Antibacterial and antibiofilm evaluation

Table 2. Common evaluation parameters for antibiotic-loaded hydrogels

Parameter	Purpose	Typical approach	Interpretation
Appearance/homogeneity	Detect phase separation, aggregation, visible instability	Visual inspection	Early formulation screening
pH	Assess local compatibility and drug stability	pH meter	Application suitability
Swelling ratio	Measure fluid uptake and network expansion	Gravimetric method	Wound exudate handling; release behavior
Gelation time	Determine transition from precursor to gel	Visual/rheological method	Injectable/in situ systems
Viscosity/rheology	Characterize flow and viscoelasticity	Rotational rheometer/viscometer	Handling and structural recovery



FTIR/thermal analysis	Assess chemical interactions and thermal behavior	FTIR/DSC/TGA	Compatibility and formulation characterization
SEM/morphology	Characterize surface and pore architecture	SEM/cryo-SEM when available	Network structure
Drug loading/entrapment	Quantify incorporated active	UV/HPLC or validated assay	Dose reproducibility
In vitro release	Characterize release profile	Dialysis/diffusion/dissolution method	Release duration and kinetics
Antibacterial activity	Assess growth inhibition/killing	MIC/MBC/zone/time-kill	Biological efficacy
Biofilm activity	Assess activity against established biofilms	Validated biofilm assay	Relevance to chronic/local infection
Stability	Monitor changes during storage	Appearance, pH, assay, activity	Shelf-life and handling

6. COMBINATION AND SYNERGISTIC ANTIBIOTIC-HYDROGEL STRATEGIES

6.1 Rationale for combination approaches

Combination systems are attractive when a single antimicrobial mechanism is insufficient. A second component may provide an independent antibacterial mechanism, improve activity against biofilms, alter membrane permeability, or modulate release. Combination design should be based on a defined mechanistic hypothesis and should be evaluated against appropriate controls, including each component alone, the hydrogel without active agents, and the combined formulation.

6.2 Dual-antibiotic systems

The gellan-gum vancomycin/clindamycin system illustrates a dual-antibiotic strategy for MRSA-associated diabetic wounds.¹⁴ The hydrogel delivered both agents locally and was evaluated in vitro and in vivo. The study is relevant because localized combination therapy can address situations in which more than one antimicrobial spectrum or mechanism is desirable, while the

carrier can moderate release and reduce repeated dosing.

6.3 Antibiotic-enzyme and antimicrobial-material combinations

Enzymes such as lysozyme provide a mechanistically different antibacterial action from many conventional antibiotics because lysozyme can hydrolyze susceptible peptidoglycan structures. Recent supramolecular lysozyme-containing hydrogel research has explored activity against drug-resistant pathogens and biofilm formation.²¹ Such systems are of interest for localized therapy, but the biological activity and stability of the enzyme must be maintained during formulation, storage, sterilization, and release.

Metal ions and metal or metal-oxide nanoparticles have also been incorporated into hydrogel networks. Silver, gold, zinc oxide, copper oxide, titanium dioxide, and magnesium oxide have been investigated in antimicrobial hydrogel systems.²² These materials can provide multiple antimicrobial mechanisms, but their use requires careful assessment of concentration-dependent



cytotoxicity, ion release, tissue compatibility, long-term stability, and regulatory acceptability.

6.4 Evaluating synergy

Synergy should be demonstrated experimentally rather than inferred from the presence of two antimicrobial components. Checkerboard microdilution and calculation of the fractional inhibitory concentration index are commonly used approaches. Time-kill experiments provide complementary information about the rate and extent of bacterial killing. Sopirala et al. compared Etest, checkerboard, and time-kill methods in

multidrug-resistant *Acinetobacter baumannii*, illustrating that the method selected can influence the observed classification of interactions.²⁰

For hydrogel systems, additional complexity arises because the carrier changes local concentrations and diffusion. A formulation may appear synergistic because one component changes release of another rather than because of a direct pharmacodynamic interaction. Therefore, synergy experiments should ideally compare free agents, hydrogel-loaded agents, blank hydrogel, and single-agent hydrogels under comparable exposure conditions.

Table 3. Representative combination strategies in antibiotic-hydrogel systems

Strategy	Representative components	Potential application	Rationale	Important control
Dual antibiotic hydrogel	Vancomycin + clindamycin / gellan gum	MRSA-infected diabetic wound	Controlled local release; antibacterial activity	Test each antibiotic alone and combined
Antibiotic + chitosan	Gentamicin + chitosan network	Wound dressing	Combines antibiotic with cationic polymer activity	Control for polymer-only effect
Antibiotic + enzyme	Antibiotic + lysozyme-containing hydrogel	Drug-resistant/biofilm-associated infection	Different antibacterial mechanisms	Preserve enzyme activity during processing
Antibiotic + inorganic component	Antibiotic/metal or metal-oxide hydrogel	Localized wound/surface infection	Multiple antimicrobial mechanisms	Assess cytotoxicity and ion release
Combination assessment	Two antimicrobial agents + hydrogel	Resistance-focused studies	Checkerboard and time-kill characterization	Interpret synergy with exposure and diffusion in mind

7. CHALLENGES AND FUTURE PERSPECTIVES

7.1 Reproducibility and scale-up

A major challenge in hydrogel development is transferring a laboratory formulation to a reproducible manufacturing process. Small changes in polymer molecular weight, degree of deacetylation, concentration, cross-linker ratio, mixing energy, temperature, pH, and hydration



can alter network structure and drug release. Quality-by-design principles can be used to define critical material attributes and critical process parameters, followed by statistically supported optimization.

7.2 Sterilization and stability

Sterilization can be particularly difficult when the hydrogel contains a biological molecule such as lysozyme, peptides, proteins, or cells. Heat, radiation, chemical sterilants, and aseptic processing may have different effects on polymer structure and biological activity. Stability studies should monitor not only physical appearance and pH but also drug content, degradation products where relevant, rheological properties, release behavior, and antimicrobial activity.

7.3 Translation from in vitro to in vivo models

In vitro antibacterial activity is necessary but not sufficient to establish therapeutic benefit. Wound fluid, proteins, tissue binding, immune responses, oxygen gradients, extracellular matrix, and polymicrobial communities can alter antimicrobial performance. Animal models provide additional evidence but also have limitations in reproducing human wound biology. Consequently, studies should use clinically relevant endpoints and clearly state the limitations of the model.

7.4 Regulatory and clinical considerations

Antibiotic-loaded hydrogels may involve characteristics of both drug products and medical devices, depending on composition, intended use, and jurisdiction. A combination product may require additional characterization of each component and of the final system. Dose uniformity, release specifications, residual cross-linking reagents, extractables and leachables,

sterility, packaging, and shelf life must be considered during development.

7.5 Smart and responsive systems

Future systems are likely to integrate controlled release with sensing or responsiveness to infection-associated conditions. pH, enzymes, temperature, reactive oxygen species, and bacterial metabolites can serve as potential triggers. The goal is not simply faster release but better matching between drug availability and the biological state of the infection. Such systems should be evaluated with realistic infection models and should demonstrate that the trigger produces a meaningful therapeutic advantage rather than only a measurable change in release kinetics.

7.6 Personalized and site-specific delivery

The anatomical site strongly influences hydrogel design. Ocular formulations require transparency, appropriate hydration, and ocular compatibility; wound dressings require fluid handling and mechanical integrity; periodontal systems may require injectability and retention in a confined pocket; and bone-associated delivery may require structural integration with a regenerative scaffold. This site-specific perspective supports the development of specialized hydrogel architectures rather than a universal formulation platform.

7.7 Research gaps

Important gaps include standardized methods for comparing hydrogel antibacterial performance, harmonized biofilm models, long-term stability data, scalable manufacturing studies, and controlled clinical investigations. Reporting should include sufficient formulation detail to permit replication. For combination systems, mechanistic evidence should accompany claims of synergy, and the contribution of the hydrogel



matrix itself should be distinguished from the contribution of the antimicrobial agents.

8. CONCLUSION

Antibiotic-loaded hydrogels provide a versatile strategy for localized antimicrobial delivery in the setting of increasing AMR and biofilm-associated infection. Their principal value lies in the ability to combine a hydrated, conformable polymer network with controlled local release of an antimicrobial agent. Evidence across chitosan, poly(vinyl alcohol), silk, gellan gum, PEG-based, dendrimer, and composite systems demonstrates that polymer chemistry and network architecture can be adapted to different antibiotics and anatomical targets. Combination strategies involving multiple antibiotics, enzymes, or antimicrobial inorganic components may broaden antibacterial mechanisms, but their effectiveness must be demonstrated with appropriate controls and clinically relevant models. Future progress will depend on reproducible manufacturing, validated analytical and microbiological methods, stability and sterilization strategies, and stronger translation from formulation studies to well-designed in vivo and clinical investigations.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest related to the publication of this review.

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