Research paper

Macrocyclic Peptide-Guided Hydrogels for Localized mRNA Delivery: Navigating Formulation Barriers to Enhance Target-Tissue Accumulation and Translation Efficacy

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Abstract

Messenger RNA (mRNA) therapeutics have considerable potential for tissue regeneration, immuno-oncology, and site-specific gene modulation; however, their clinical application is limited by rapid degradation, inefficient cellular uptake, endosomal entrapment, short tissue residence, and undesirable hepatic accumulation after systemic administration. Macrocyclic peptide-guided hydrogels represent an advanced localized delivery strategy designed to overcome these formulation and physiological barriers. Injectable hydrogels can function as biodegradable depots that protect mRNA-loaded lipid nanoparticles or polyplexes from nucleases, minimize systemic diffusion, and provide sustained, spatially controlled release at the target site. Their shear-thinning, self-healing, and stimuli-responsive properties facilitate minimally invasive administration while maintaining depot integrity and regulating cargo liberation through diffusion- and degradation-controlled mechanisms. Macrocyclic peptides contribute high-affinity and selective recognition of tissue-specific receptors, extracellular-matrix components, or tumor-associated antigens because of their conformational rigidity, proteolytic stability, and reduced binding entropy. When covalently integrated into hydrogel networks or displayed on nanocarrier surfaces, these peptides enhance target-tissue retention, receptor-mediated endocytosis, and intracellular delivery. Additional incorporation of ionizable lipids, fusogenic peptides, and pH-responsive components may improve endosomal escape and cytosolic mRNA release, thereby increasing translational efficiency. Despite these advantages, optimization remains necessary regarding rheological behavior, mesh size, nanoparticle stability, burst release, immunogenicity, biodegradation, manufacturing reproducibility, sterilization, and regulatory compliance.

Keywords: Macrocyclic peptides, Injectable hydrogels, Localized mRNA delivery, Endosomal escape, Targeted nanomedicine.

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INTRODUCTION

Messenger RNA therapeutics have transitioned from proof-of-concept to clinical reality, yet their pharmacological utility remains constrained by delivery architectures that prioritize systemic administration and consequently funnel payloads toward hepatic clearance rather than disease-relevant microenvironments, thereby necessitating a paradigm shift toward localized, retention-anchored depots that can sustain bioavailability while circumventing off-target sequestration (Tenchov et al., 2021). Standard lipid nanoparticles (LNPs), despite their clinical validation for vaccine and liver-targeted applications, exhibit pronounced biodistribution biases wherein apolipoprotein E adsorption, opsonization, and reticuloendothelial system (RES) recognition drive rapid hepatic and splenic accumulation, limiting extrahepatic bio-distribution and elevating risks of hepatotoxicity, cytokine release, and dose-limiting inflammatory responses upon repeated or high-dose administration (Sosnik et al., 2017). Even

following ostensibly local routes such as intramuscular or intratumoral injection, a substantial fraction of LNPs diffuses into systemic circulation within hours, recapitulating liver-tropic behavior and undermining the intended spatial confinement of translation, which is particularly detrimental for indications requiring sustained, high local protein expression such as tissue regeneration, immuno-oncology, or site-specific gene editing (Rafael et al., 2021). These systemic delivery bottlenecks characterized by low target-tissue residence time, subtherapeutic local concentrations, and off-target organ exposure create a compelling rationale for engineering hydrogel-based depots that physically retain mRNA-loaded nanocarriers at the administration site, thereby extending the local exposure window, reducing systemic spillover, and enabling controlled release kinetics that align with the temporal demands of translational machinery (Thang et al., 2023). Hydrogels, as three-dimensional, hydrophilic polymer networks, offer tunable mesh sizes, degradability profiles, and rheological properties that can be optimized to encapsulate LNPs or other nucleic acid carriers while shielding them from nuclease degradation and premature clearance, effectively functioning as a kinetic buffer that decouples injection from systemic distribution (Zeimaran et al., 2021). However, passive retention alone is insufficient to guarantee efficient cellular uptake and robust translation, especially in fibrotic, hypoxic, or immunosuppressive microenvironments where endosomal escape and ribosomal engagement may be impaired by endoplasmic reticulum stress or altered trafficking pathways (Gulrez et al., 2011). This limitation motivates the integration of macrocyclic peptides rigidified, conformationally constrained scaffolds with high binding affinity and selectivity for tissue-specific receptors or extracellular matrix components into the hydrogel matrix or onto the surface of encapsulated nanocarriers, thereby creating a synergistic platform wherein physical depot behavior is complemented by active, high-avidity targeting that promotes receptor-mediated endocytosis, enhances local cellular internalization, and potentially biases intracellular routing toward productive translation rather than lysosomal degradation (Akhtar et al., 2016). Macrocyclic peptides, by virtue of their preorganized topology and reduced entropic penalty upon binding, can achieve nanomolar affinities for integrins, growth factor receptors, or tumor-associated antigens, and when presented in a multivalent fashion from a hydrogel scaffold, they can exploit avidity effects to further amplify local accumulation and retention at the target tissue interface (Ali et al., 2022). The resulting macrocyclic peptide-guided hydrogel platform thus embodies a dual-function design: the hydrogel component ensures sustained, localized release and protection of mRNA cargo, while the macrocyclic peptide component confers spatial precision and cellular selectivity, collectively navigating formulation barriers such as nuclease susceptibility, rapid clearance, and inefficient endosomal escape that have historically limited the efficacy of localized mRNA delivery (Lavrentev et al., 2023). The figure 1 illustrate different nanocarrier platforms, including liposomes, micelles, nanoparticles, cyclic peptides, dendrimers, hydrogels, and microneedles, for acute and chronic wound management. It highlights stimuli-responsive approaches using pH, temperature, light, ultrasound, and electroporation to enhance controlled drug delivery at the wound site.

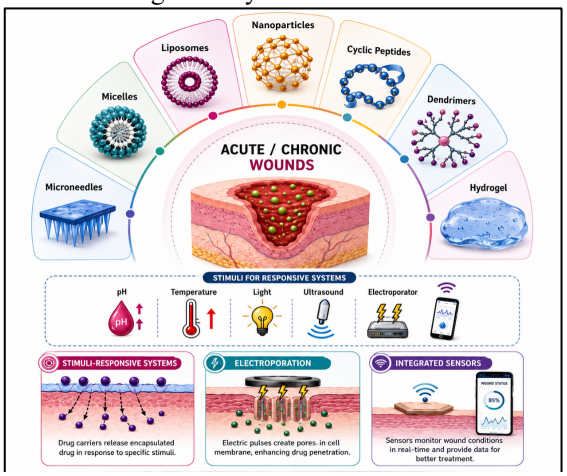

Figure 1: Advanced Nanocarrier Systems and Smart Technologies for Targeted Wound Drug Delivery

Formulation & Physiological Barriers

Formulation and physiological barriers to localized mRNA delivery via macrocyclic peptide-guided hydrogels span a tightly coupled hierarchy of extracellular, interfacial, and intracellular constraints that collectively dictate biodistribution, cargo integrity, and translational output (Toews et al., 2023). Mechanically, injectable hydrogels must reconcile syringeability with post-injection structural integrity: the material should exhibit pronounced shear-thinning so that viscosity (η) drops sufficiently at high shear rates ($\approx$1–10 s^{-1}) to permit extrusion through fine-gauge needles (25-27 G) yet recover a high storage modulus (G') at rest to maintain depot shape fidelity and resist rapid dispersion in the interstitial space (Siepmann et al., 2001). This rheological duality is essential because excessive crosslink density or stiff networks can impede extrusion and generate high shear stresses that damage encapsulated mRNA–lipid nanoparticles (LNPs) or polyplexes, while overly soft gels may collapse under tissue pressure, leading to burst release and loss of localization (Li et al., 2016). Simultaneously, the extracellular matrix (ECM) imposes steric and diffusive constraints: the mesh size of collagen- and proteoglycan-rich tissues can restrict nanoparticle

mobility, especially for particles whose hydrodynamic diameter approaches or exceeds the effective pore size of the ECM, thereby limiting penetration depth and target-cell engagement unless the hydrogel is engineered to locally remodel or transiently loosen the matrix (Ávila-Salas et al., 2020). Enzymatically, the extracellular milieu is rich in ribonucleases that rapidly hydrolyze exposed RNA, imposing severe half-life ($t_{1/2}$) limitations on free mRNA; even within LNPs, surface defects, PEG shedding, or incomplete encapsulation can expose vulnerable regions, accelerating decay unless additional stabilization strategies such as nucleoside modifications (e.g., 2′-O-methyl, 2′-fluoro), optimized 5′ caps and poly(A) tails, or protective hydrogel matrices are employed to extend functional $t_{1/2}$ and preserve sequence integrity (Siboro et al., 2021). At the nano–bio interface, maintaining mRNA LNP or polyplex stability under hydrogel crosslinking conditions is critical: chemical crosslinkers, radical initiators, or pH shifts used during gelation can perturb lipid packing, induce premature cargo leakage, or alter surface charge, compromising colloidal stability and cellular uptake; similarly, mechanical shear during injection can deform or fragment LNPs, especially if they lack reinforcement strategies such as post-assembly crosslinking with acid-cleavable linkers that stabilize particles during storage and administration but disassemble in the mildly acidic endosome to facilitate escape (Correa et al., 2021). The hydrogel itself can mitigate some of these stresses by providing a hydrated, sterically protective microenvironment that reduces nuclease access and dampens shear transmission to the payload, but this requires careful tuning of network density, degradation kinetics, and interactions with the nanocarrier surface to avoid sequestration or aggregation (Andrade et al., 2021). Once internalized, intracellular barriers dominate: endosomal sequestration remains a primary bottleneck, as the majority of internalized LNPs or polyplexes are trafficked to lysosomes and degraded unless they efficiently escape via endosomal membrane destabilization, often governed by the ionizable lipid pKa (ideally 6.2–6.9) and the capacity to undergo protonation-driven structural rearrangements in the acidic endosome (Cao et al., 2019). In local tissue microenvironments, especially inflamed or damaged sites, pattern recognition receptors (PRRs) such as Toll-like receptors (TLR3, TLR7/8), RIG-I, and MDA5 can sense exogenous RNA or lipid components, triggering innate immune signaling that may reduce translational efficiency, induce cytokine release, or promote clearance by resident macrophages and dendritic cells (Wang et al., 2023).

Table 1: Stimuli-Responsive Peptide- and Antibody-Based Hydrogels for Cancer Therapy

Category	Hydrogel / Material	Stimulus	Model	Application	Ref.
Peptides	PBA-grafted chitosan/PEDOT nanocomposite	Electrical, pH	PC-3, PNT-2 cells	Prostate cancer	(Asadi et al., 2024)
Peptides	Ac-I3SLKG-NH_2 hydrogel	Enzyme	HeLa, NIH 3T3 cells	Cancer	(Correa et al., 2021)
Peptides	Chlorambucil–tyroservatide self-assembled hydrogel	-	MCF-7, BEL-7402, HepG2-bearing mice	Breast & liver cancer	(Siboro et al., 2021)
Peptides	Melittin-RADA28 (MR) hydrogel	Enzyme	CT26-bearing mice	Colon carcinoma	(Li et al., 2016)
Peptides	NapGDFDFDYGYSV (D-YSV) hydrogel	-	BEL-7402-bearing mice	Hepatoma	(Tows et al., 2023)
Monoclonal antibodies	Vitamin E-functionalized ABA triblock copolymer	-	BT474-bearing mice	Breast cancer	(Ali et al., 2022)
Monoclonal antibodies	Thiolated hyaluronic acid hydrogel	Redox	NA	Cancer	(Thang et al., 2023)
Monoclonal antibodies	γ-PGA-MA/4-arm PEG-SH hydrogel	-	BT474-bearing NOD/SCID mice	Breast cancer	(Rafael et al., 2021)

Macrocyclic Peptides as High-Affinity Guidance Vectors

Macrocyclic peptides function as high-affinity guidance vectors by exploiting a unique

physicochemical regime that bridges small molecules and biologics, wherein conformational constraint, encoded by head-to-tail cyclization or side-chain stapling, preorganizes the backbone into bioactive topologies that minimize entropic penalties upon target engagement, thereby enabling sub-nanomolar dissociation constants (K_D) against challenging epitopes such as shallow protein–protein interaction interfaces, extracellular domain grooves, and glycosylated cell-surface markers that are often refractory to conventional small-molecule ligands (Hajareh Haghighi et al., 2023). This conformational rigidity, arising from restricted φ/ψ dihedral freedom and stabilized secondary structural motifs (e.g., β-hairpins, type II′ turns, and helical turns), not only enhances binding specificity but also confers marked proteolytic stability relative to linear analogues by eliminating free N- and C-termini susceptible to exopeptidases and by sterically occluding endopeptidase access to scissile bonds, resulting in serum half-lives that can exceed those of linear peptides by one to two orders of magnitude and enabling sustained target-tissue residence within hydrogel depots (Liscano et al., 2020). The de novo discovery of such macrocycles is now routinely achieved through mRNA display platforms, particularly the Random nonstandard Peptides Integrated Discovery (RaPID) system, which couples genetic code reprogramming with in vitro translation to generate libraries of >10^12 unique macrocyclic sequences containing noncanonical amino acids (e.g., N-methylated residues, α-hydrazino acids) that further rigidify conformation and enhance metabolic stability, followed by iterative affinity selection against recombinant extracellular domains or native cell-surface receptors expressed on live cells (RaPID-ExCells), enabling the isolation of ligands with single-digit nanomolar to sub-nanomolar affinities and built-in selectivity against off-target isoforms (Ghaly et al., 2023). These selection campaigns yield sequence-defined macrocycles that can be engineered with orthogonal functional handles such as azides, alkynes, or aminooxy groups positioned at solvent-exposed loops or termini without perturbing the binding epitope, thereby facilitating site-specific bioconjugation to hydrogel scaffolds or mRNA carrier surfaces via bioorthogonal chemistries that proceed under physiological conditions with high fidelity and minimal cross-reactivity (Zhang et al., 2021). For hydrogel integration, strain-promoted azide–alkyne cycloaddition (SPAAC) between azide-functionalized macrocycles and dibenzocyclooctene (DBCO)-modified polysaccharide or peptide-based networks (e.g., hyaluronic acid, gelatin methacryloyl) enables rapid, catalyst-free covalent tethering that preserves macrocycle orientation and accessibility while preventing leaching during depot erosion, whereas oxime ligation between aminooxy-bearing macrocycles and aldehyde-functionalized polymer backbones offers an alternative water-compatible route that generates stable C=N bonds with concomitant release of water, ideal for pH-sensitive hydrogel systems designed for tumor-microenvironment-triggered release (Kordi et al., 2023). In contrast, when macrocycles are deployed as surface ligands on mRNA-loaded lipid nanoparticles or polyplexes embedded within hydrogels, the same bioorthogonal handles permit conjugation to ionizable lipid headgroups or PEG chains via heterobifunctional linkers, creating a dual-function architecture wherein the hydrogel provides sustained local release and nuclease shielding while the macrocycle guides cellular uptake via receptor-mediated endocytosis, thereby enhancing target-tissue accumulation and translational output by concentrating mRNA payloads at disease-relevant cell populations (Resina et al., 2024).

Hydrogel Architecture & Controlled mRNA Release Mechanics

Matrix material selection for mRNA-delivering hydrogels prioritizes viscoelastic architectures that combine shear-thinning injectability with self-healing network reformation, thereby enabling minimally invasive deposition followed by rapid recovery of elasticity-dominated behavior (G′ > G″) that resists convective clearance while maintaining mesh sizes commensurate with mRNA nanocomplex dimensions (typically 50–200 nm) (Chen et al., 2017). Shear-thinning arises from reversible physical cross-links such as host–guest complexes, coiled-coil associations, or dynamic covalent bonds (e.g., imines, disulfides, boronate esters) that dissociate under high strain rates during syringe extrusion, transiently lowering viscosity by several orders of magnitude, then re-associate upon cessation of shear to restore gel integrity within seconds to minutes, a process quantifiable via three-interval thixotropy tests and essential for preventing backflow or leakage post-injection (Yang et al., 2019). Dynamic covalent chemistries further impart stimuli-responsiveness: pH-labile linkages (hydrazones, acetals) undergo acid-catalyzed hydrolysis in tumor microenvironments (pH 6.5–6.9) or endosomal compartments (pH 5.0–6.0), accelerating network degradation and cargo liberation, while matrix metalloproteinase (MMP)-cleavable peptide cross-linkers (e.g., GPLG↓VG, PVGLIG) are selectively hydrolyzed by MMP-2/9 overexpressed in malignant or inflamed tissues, coupling release kinetics to local enzymatic activity and achieving up to 3–5-fold higher bioavailability versus monoresponsive systems (Liu et al., 2022). Spatiotemporal release of mRNA nanocomplexes is governed by the interplay between diffusion-controlled transport, dictated by hydrogel mesh size (ξ) relative to nanoparticle hydrodynamic diameter

(d_h) according to the obstruction-scaling model, and matrix-degradation-controlled erosion, wherein bulk or surface degradation modulates time-dependent increases in ξ and concomitant reductions in diffusional barriers, enabling biphasic release profiles characterized by an initial diffusion-dominated phase followed by degradation-accelerated liberation that can be tuned via cross-link density, polymer molecular weight, and cleavable linker stoichiometry (Wilkinson et al., 2020). Diffusion-controlled release predominates in non-degradable or slowly degrading networks, yielding near-zero-order kinetics when ξ ≈ d_h, whereas matrix-degradation-controlled release emerges in enzyme- or pH-sensitive hydrogels, producing sigmoidal or pulsatile profiles that align payload availability with disease-relevant biological windows, such as post-surgical recurrence risk periods or immunotherapy priming phases (Falcone et al., 2021). Localized tissue retention is optimized by rheological parameters that balance storage modulus (G′), loss tangent (tan δ = G″/G′), and stress relaxation time (τ): elevated G′ (>100 Pa) and low tan δ (<0.3) minimize rapid clearance by interstitial flow or lymphatic drainage, while intermediate τ (10–100 s) permits network rearrangement that mitigates burst release by allowing embedded nanocomplexes to re-embed during early-phase swelling, reducing initial fractional release from >40% to <15% without compromising cumulative delivery over days to weeks (Malone et al., 2017). Burst-release toxicity, arising from sudden high local concentrations of ionizable lipids or cationic polymers that disrupt cell membranes or provoke innate immune activation, is further attenuated by incorporating charge-shielding moieties (e.g., zwitterionic polymers, PEG spacers) within the hydrogel matrix and by engineering gradient cross-linking that creates a dense outer shell to retard initial efflux while maintaining a porous core for sustained release, strategies that collectively enhance biocompatibility and therapeutic index in vivo (Carter et al., 2023).

Table 2: Therapeutic Potential and Limitations of Antimicrobial Peptides in Chronic Wound Healing

AMPs: Key Features / Limitations	**Chronic Wound Challenge**	**Healing Phase / Approach**	**Ref.**
Potent activity against ESKAPE pathogens; modified AMPs may help minimize host toxicity	Biofilm-mediated resistance in *S. aureus* and *P. aeruginosa*	Inflammation – Anti-biofilm therapy	(Wang et al., 2022)
Enhance innate defense, but their endogenous production may decline in diabetes	Cellular senescence and reduced keratinocyte migration	Proliferation – Cell migration	(Huan et al., 2020)
Limited by rapid degradation, proteolysis and pH-dependent instability	Enzymatic breakdown and elevated oxidative stress	Multiphase – Nanocarrier delivery	(Overhage et al., 2008)
Broad antimicrobial action through membrane disruption and intracellular targets	Increasing antimicrobial resistance and limited new antibiotics	Inflammation – Pathogen clearance	(Su et al., 2025)
Combined use with antibiotics may enhance efficacy and reduce drug requirements	Multidrug-resistant bacterial infections	Inflammation – Combination therapy	(Szeglet es et al., 2011)
Promote M2 macrophage polarization and inflammatory	Sustained M1-dominant inflammation in chronic wounds	Inflammation/Proliferation – Immunomodulation	(Malone et al., 2017)

resolution			

Mechanistic Pathways: Cellular Uptake to Protein Expression

Receptor-Mediated Endocytosis

Macrocyclic ligand engagement initiates cellular internalization through high-affinity, conformationally preorganized binding to overexpressed surface receptors such as α_vβ_3 integrins, somatostatin GPCRs, or transferrin receptors, triggering clathrin- or caveolin-dependent endocytic pathways that route ligand–receptor complexes into early endosomes (pH ~6.5) within 5–15 minutes post-exposure (Wu et al., 2025). Upon macrocycle binding, receptor clustering recruits adaptor proteins (e.g., AP-2, epsin) and dynamin GTPases that mediate vesicle scission, followed by Rab5-positive early endosome maturation and subsequent sorting toward either Rab7-positive late endosomes/lysosomes for degradation or recycling endosomes for surface re-expression, a trajectory that can be biased by macrocycle valency and off-rate kinetics to favor productive trafficking over lysosomal clearance (Zhang et al., 2021). The spatial orientation of macrocycles on hydrogel-embedded carriers further modulates avidity effects, where multivalent presentation enhances local receptor occupancy and accelerates internalization rates (k_endocytosis) while minimizing off-target uptake by non-expressing cell populations, thereby improving the therapeutic index of localized mRNA depots (Campos et al., 2025).

Endosomal Escape Enhancements

Endosomal entrapment remains the principal efficiency bottleneck for mRNA therapeutics, with <5% of internalized cargo typically achieving cytosolic release; co-formulation strategies within hydrogel matrices address this by incorporating fusogenic lipids (e.g., DOPE, ionizable lipids with pK_a ~6.4) and pH-sensitive peptides (e.g., INF7, pHLIP, HA2-derived sequences) that undergo protonation-driven conformational transitions in acidifying endosomes to destabilize the limiting membrane (Xiao et al., 2022). Ionizable lipids become cationic at endosomal pH, inducing a lamellar-to-hexagonal (H_II) phase transition that promotes membrane fusion and transient pore formation, while fusogenic peptides insert their amphipathic α-helices into the bilayer to generate curvature stress and osmotic imbalances that rupture the endosomal envelope (Yasir et al., 2018). Recent advances include de novo designed pH-responsive peptides that self-assemble into 2–10 nm nanoscale pores within acidified membranes, directly enabling macromolecular escape without reliance on indirect osmotic swelling mechanisms, and thioester-containing ionizable lipids that combine enhanced endosomal escape with acid-labile biodegradability to reduce accumulation toxicity upon repeated dosing. Embedding these enhancers within hydrogel scaffolds ensures sustained local availability during depot erosion, maintaining a high local concentration of escape-promoting moieties that synergize with macrocycle-guided uptake to maximize cytosolic mRNA delivery (Li et al., 2022).

Quantitative Spatial Translation

Mapping local versus systemic protein expression requires multiparametric quantification of peak concentration (C_max), duration of detectable translation (t_1/2,expr), and tissue penetration depth (δ_tissue), typically achieved through longitudinal imaging (e.g., bioluminescence, PET with ^18F-labeled amino acid analogs) coupled with ex vivo mass spectrometry or ELISA of microdissected tissue sections (Mangoni et al., 2016). C_max reflects the maximal local protein output per unit tissue volume, often normalized to administered mRNA dose and hydrogel depot size, while t_1/2,expr captures the functional persistence of translation before mRNA degradation or immune clearance terminates expression, with hydrogel-mediated sustained release extending this window from hours to days relative to bolus injections (Pfalzgraff et al., 2018). Tissue penetration depth (δ_tissue) is quantified via confocal or two-photon microscopy of fluorescent reporter proteins expressed from delivered mRNA, revealing gradients of expression that decay exponentially from the hydrogel–tissue interface, with macrocycle guidance sharpening this gradient by concentrating uptake in receptor-positive cell layers (Wilkinson et al., 2023). Spatial transcriptomics and single-cell RNA-seq further resolve heterogeneity in translation efficiency across cell subpopulations, enabling correlation of macrocycle receptor density with local protein output and informing iterative optimization of ligand affinity and carrier architecture to achieve target-tissue accumulation with minimal systemic spillover (Haidari et al., 2023).

Translational Bottlenecks & Clinical Roadmap

Translational bottlenecks for macrocyclic peptide-guided hydrogel-mRNA hybrids center on scalable, GMP-compliant manufacturing and comprehensive toxicology-immunogenicity profiling, both of which dictate regulatory feasibility and clinical adoption. Scale-up requires robust, modular processes that ensure batch-to-batch reproducibility across multi-component systems wherein hydrogel precursors (e.g., recombinant proteins, synthetic polymers), macrocyclic peptides (often containing noncanonical residues), and mRNA-loaded nanocarriers (LNPs or polyplexes) must be integrated with precise stoichiometry, spatial organization, and functional integrity (Min et al., 2024). Critical process parameters include mixing dynamics (often microfluidic for nanoparticle

formation), conjugation efficiency (bioorthogonal reactions such as SPAAC or oxime ligation), gelation kinetics, and sterilization compatibility, all of which influence critical quality attributes like particle size distribution, zeta potential, peptide grafting density, mRNA encapsulation efficiency, and release kinetics (Alberts et al., 2025). Variability in polymer molecular weight, lipid composition, peptide purity, or mRNA integrity can propagate into heterogeneity in depot erosion profiles and translational output, complicating comparability protocols and necessitating stringent in-process controls and orthogonal analytics (e.g., SEC-MALS, DLS, HPLC-MS, qRT-PCR) (Zhu et al., 2025). GMP alignment further demands defined raw material sourcing (e.g., endotoxin-free, animal-component-free reagents), closed-system processing to minimize contamination risk, and validated lyophilization or cold-chain strategies for mRNA stability, with emerging platforms leveraging single-use bioreactors and automated microfluidics to enhance scalability while maintaining product consistency (Gonçalves et al., 2025). Toxicology and immunogenicity assessments must address three interrelated domains: synthetic macrocycles, hydrogel degradation products, and chronic local tissue responses (Adnan et al., 2025). Macrocyclic peptides, despite enhanced proteolytic stability, may harbor neoepitopes from noncanonical amino acids or sequence modifications that trigger T-cell responses or anti-drug antibody formation, necessitating in silico HLA-binding predictions, ex vivo T-cell activation assays, and repeat-dose immunogenicity studies in relevant species (Zhang et al., 2025). Hydrogel degradation fragments ranging from oligomeric hyaluronic acid and PEG derivatives to peptide crosslink remnants can act as immunomodulatory cues, polarizing macrophages toward pro-inflammatory ($CD80^+/CD86^+$) or reparative phenotypes depending on degradation kinetics and local enzymatic activity, with nondegradable or slowly eroding networks risking chronic inflammation, fibrotic encapsulation, or foreign-body giant cell formation (Dong et al., 2025).

CONCLUSION

Macrocyclic peptide-guided hydrogels represent a promising and multifunctional platform for localized mRNA delivery, effectively addressing critical formulation and physiological barriers that have limited the therapeutic potential of mRNA-based interventions. By combining the sustained-release and protective properties of injectable hydrogels with the high-affinity, tissue-specific targeting capabilities of macrocyclic peptides, this strategy enables enhanced target-tissue accumulation, reduced systemic spillover, and improved translational efficiency. The hydrogel matrix provides a hydrated, biocompatible microenvironment that shields mRNA-loaded nanocarriers from nuclease degradation, minimizes burst release, and regulates cargo liberation through diffusion- and degradation-controlled mechanisms. Meanwhile, macrocyclic peptides confer conformational rigidity, proteolytic stability, and selective receptor engagement, promoting receptor-mediated endocytosis and biasing intracellular trafficking toward productive translation rather than lysosomal degradation. Integration of ionizable lipids, fusogenic peptides, and pH-responsive components further enhances endosomal escape and cytosolic mRNA availability, thereby maximizing protein expression at the disease site. Despite these advantages, several challenges must be addressed before clinical translation, including optimization of rheological properties, mesh size, nanoparticle stability, immunogenicity, biodegradation kinetics, manufacturing reproducibility, sterilization compatibility, and regulatory compliance. Standardized preclinical models, robust analytical methods, and scalable GMP-compatible processes are essential to ensure batch-to-batch consistency, safety, and efficacy. Future research should focus on refining macrocycle design, hydrogel architecture, and nanocarrier integration to achieve precise spatiotemporal control over mRNA release and expression.

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