

REVIEW ARTICLE

Nanocarriers for Peptide-Based Therapeutics Against Sexually Transmitted Vaginal Infections

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ABSTRACT

Nanocarrier-based peptide therapeutics offer a promising strategy to combat sexually transmitted vaginal infections, including bacterial vaginosis, vulvovaginal candidiasis, trichomoniasis, and other STIs that are often recurrent and inadequately managed by conventional therapies. Antimicrobial and immunomodulatory peptides provide broad-spectrum activity against bacterial, fungal, and viral pathogens but are limited by poor stability, enzymatic degradation, low bioavailability, and potential toxicity in the vaginal environment. Encapsulation in nanocarriers such as liposomes, polymeric nanoparticles, nanogels, micelles, and dendrimers can protect peptides, enhance mucoadhesion or mucus penetration, prolong residence time, and enable controlled or stimuli-responsive release at the site of infection.

This review summarizes the pathophysiology of sexually transmitted vaginal infections and the roles of key pathogens, biofilms, mucus barriers, and antimicrobial resistance in limiting current treatments. It discusses the mechanisms, advantages, and limitations of antimicrobial peptides, with emphasis on formulation and design strategies to enhance their stability, selectivity, and safety for intravaginal use. Recent advances in vaginally targeted nanocarrier platforms and preclinical in vitro, ex vivo, and in vivo evidence demonstrating improved efficacy, tissue coverage, retention, and biocompatibility of peptide-loaded systems are highlighted. Remaining challenges in large-scale manufacturing, long-term safety, and regulatory approval, as well as future opportunities for smart and potentially personalized nanocarrier-peptide systems, are outlined to guide translation toward clinical application.

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INTRODUCTION

Sexually transmitted vaginal infections such as bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis affect a large proportion of women worldwide and are associated with substantial physical, emotional, and economic burdens. Bacterial vaginosis arises from disruption of the normal vaginal microbiota and overgrowth

of anaerobic bacteria, candidiasis is driven by excessive proliferation of *Candida* species, and trichomoniasis, the most common non-viral sexually transmitted infection, is caused by *Trichomonas vaginalis* and often manifests with pruritus, burning, and abnormal discharge. Despite the availability of systemic and topical antimicrobial therapies, conventional treatments remain suboptimal due to limited residence time

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in the vaginal canal, inadequate tissue penetration, and the risk of adverse effects and antimicrobial resistance[1-3].

Peptide-based therapeutics offer broad-spectrum antimicrobial activity and specificity but face inherent drawbacks, including poor physicochemical stability, short in vivo half-life, susceptibility to enzymatic degradation, and generally low bioavailability following conventional administration routes[4, 5]. Systemic administration of antimicrobial peptides can further induce off-target toxicity, immunogenic responses, and selective pressure that promotes microbial resistance[1], which altogether restricts their clinical utility for chronic or recurrent vaginal infections. These limitations underscore the need for advanced delivery systems capable of protecting peptide drugs, prolonging their local presence at the site of infection, and minimizing systemic exposure.

Nanocarrier-based vaginal delivery systems have emerged as a promising strategy to address these challenges by encapsulating peptide drugs within nanoparticles, liposomes, or nanocomposite hydrogels to shield them from enzymatic degradation while enabling controlled and sustained release at the mucosal surface[4, 6, 7]. Such nanosystems can be engineered for enhanced mucoadhesion or mucus penetration, improving retention within the vaginal canal, reducing dosing frequency, and limiting systemic side effects by concentrating the therapeutic action locally[2, 8-10]. However, successful clinical translation requires careful consideration of the complex vaginal environment, including pH, mucus turnover, microbiota composition, and potential immunogenicity of the nanomaterials, as well as rigorous demonstration of long-term safety and biocompatibility[6, 9].

VAGINAL INFECTIONS

Vaginal infections caused by sexually transmitted pathogens represent a major global health issue for women, frequently resulting in acute symptoms and long-term reproductive sequelae if not adequately treated. These infections are influenced by a dynamic interaction between the vaginal microbiome and external factors such as antibiotic exposure, hormonal fluctuations, and sexual behavior, all of which can disrupt microbial homeostasis and favor pathogen overgrowth. In addition, many of these pathogens exploit biological

barriers, including biofilms and the viscoelastic mucus layer, which impede drug penetration and contribute to persistent or recurrent disease.

Common sexually transmitted vaginal pathogens include those associated with bacterial vaginosis, where an imbalance in the vaginal microbiota leads to overgrowth of anaerobic bacteria[1, 11], and *Trichomonas vaginalis*, a protozoan responsible for trichomoniasis that induces inflammation and increases susceptibility to other sexually transmitted infections[11]. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are major bacterial agents that can ascend the reproductive tract and cause pelvic inflammatory disease, infertility, and adverse pregnancy outcomes if untreated[1]. Viral infections such as genital herpes, caused by herpes simplex virus, produce painful genital lesions and are linked to an elevated risk of HIV acquisition, further compounding the clinical burden[12].

Treatment of these infections is complicated by multiple mechanisms of persistence and resistance. Biofilm formation by bacterial and fungal communities creates a protective matrix that limits antimicrobial penetration and shields pathogens from host immune defenses[13], while the cervical–vaginal mucus layer can restrict the diffusion and retention of conventional dosage forms, thereby reducing local drug concentrations at the site of infection[14, 15]. The growing problem of antimicrobial resistance among sexually transmitted pathogens further undermines the effectiveness of standard antibiotic regimens and underscores the need for novel therapeutic approaches with distinct modes of action[16, 17].

Peptide-based antimicrobials are emerging as promising candidates because they can exhibit broad-spectrum activity, rapid bactericidal or virucidal effects, and potential selectivity for pathogenic organisms. However, several unmet needs must be addressed, including achieving sufficient stability in the protease-rich vaginal environment, optimizing local delivery to reach pathogens embedded within biofilms and mucus[16], and enhancing bioavailability through advanced formulations such as nanoparticles, hydrogels, or mucoadhesive systems[15, 18]. Rational design of peptides with targeted action against specific pathogens, while sparing beneficial lactobacilli and preserving the protective vaginal microbiota, will be critical for maximizing therapeutic benefit and minimizing dysbiosis and

recurrence[16].

PEPTIDE THERAPEUTICS

Peptide therapeutics, particularly antimicrobial peptides (AMPs) such as defensins and magainins, are emerging as promising candidates for managing vaginal infections because of their broad-spectrum activity and multi-target mechanisms of action. As key components of the innate immune system, these cationic peptides can act against bacteria, fungi, and viruses, including some drug-resistant strains, making them attractive as next-generation anti-infective agents. Nevertheless, their clinical translation is constrained by issues such as limited stability in biological fluids, potential cytotoxicity toward host cells at higher concentrations, and challenges in large-scale, cost-effective production[19].

AMPs typically exert their antimicrobial effects through membrane-active and nonlytic pathways. In many cases, they interact electrostatically with negatively charged microbial membranes, insert into the lipid bilayer, and induce pore formation or membrane disruption, leading to rapid leakage of intracellular contents and cell death, which contributes to activity against a wide spectrum of pathogens, including biofilm-forming and resistant strains. Beyond direct membrane damage, some AMPs can translocate across the membrane and bind intracellular targets such as nucleic acids or essential enzymes, thereby inhibiting replication, transcription, or metabolic pathways without immediate lysis, while others are able to interfere with quorum sensing and destabilize biofilm matrices to increase susceptibility to co-administered agents. These multifaceted mechanisms reduce the likelihood of resistance development compared with conventional antibiotics, but also necessitate careful design to avoid off-target effects on host tissues[19-22].

A major limitation of AMPs in vaginal applications is their vulnerability to enzymatic degradation and environmental factors. Proteolytic enzymes present in genital secretions can rapidly cleave peptide backbones, while variations in local pH and ionic strength can alter peptide conformation, membrane binding, and overall antimicrobial activity. To address these issues, several stabilization strategies have been investigated, including cyclization, incorporation of D-amino acids or non-natural residues, lipidation, and formulation within protective delivery systems

such as nanoparticles, liposomes, and hydrogels, which can shield AMPs from degradation and prolong their half-life at the mucosal surface[19].

Defensins and magainins exemplify the therapeutic potential and practical challenges of AMPs for vaginal use. Human defensins, classified into α -, β -, and θ -subfamilies, combine membrane-disruptive activity with immunomodulatory functions, including chemotactic effects and modulation of inflammatory responses, offering dual antimicrobial and host-defense benefits but also raising concerns about dose-dependent cytotoxicity and inflammation[23]. Magainins, originally identified in frog skin, display broad-spectrum activity primarily via membrane permeabilization and have inspired synthetic analogs, yet their moderate stability and toxicity profiles have limited direct clinical adoption[24]. Ongoing research integrating rational peptide design with nanotechnology-enabled delivery aims to reduce cytotoxicity, enhance stability and local bioavailability, and enable targeted action against vaginal pathogens while sparing beneficial microbiota, which is crucial for advancing AMPs from experimental models to safe and effective clinical therapies[25, 26].

NANOCARRIERS FOR DELIVERY

Nanocarriers have emerged as a promising strategy for delivering peptide-based therapeutics against sexually transmitted vaginal infections. These nanocarriers are designed to overcome the physiological barriers of the vaginal environment, such as mucus and pH variations, to enhance drug delivery and efficacy. The following sections describe various types of nanocarriers suitable for peptide delivery, focusing on their vaginal-specific properties like mucoadhesion and mucus penetration.

Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs, including peptides. They are known for their biocompatibility and ability to enhance the stability of encapsulated peptides[27, 28]. For vaginal delivery, liposomes can be modified to improve mucoadhesion and penetration through the mucus layer, which is crucial for effective drug delivery in the vaginal environment[1]. Studies have shown that liposomes can be engineered to release drugs in response to specific stimuli, enhancing targeted delivery and reducing systemic side effects[27].

Polymeric nanoparticles, such as those made from PLGA (poly (lactic-co-glycolic acid)) and chitosan, offer controlled release and protection of peptides from enzymatic degradation [15, 29]. These nanoparticles can be designed to exhibit mucoadhesive properties, which help in prolonging the residence time of the drug in the vaginal cavity, thereby enhancing therapeutic efficacy[30]. Chitosan, in particular, is known for its natural mucoadhesive properties and ability to open tight junctions, facilitating deeper penetration into the vaginal mucosa[15].

Nanogels are hydrophilic networks capable of swelling in aqueous environments, making them suitable for encapsulating peptides and providing a sustained release[1]. Their high water content and soft nature allow them to penetrate the mucus layer effectively, which is beneficial for vaginal drug delivery[8]. Nanogels can be engineered to respond to environmental stimuli such as pH and temperature, which can be leveraged for targeted drug release in the vaginal environment[1].

Micelles are formed by the self-assembly of amphiphilic molecules and can encapsulate hydrophobic drugs within their core[27]. They are particularly useful for delivering hydrophobic peptides and can be modified to enhance their stability and mucoadhesive properties[1]. The small size of micelles allows them to penetrate the mucus layer efficiently, making them suitable for vaginal drug delivery[8].

Dendrimers are highly branched, tree-like structures that provide a high degree of surface functionality and versatility for drug delivery. They can be engineered to enhance mucoadhesion and mucus penetration, which is critical for effective vaginal delivery of peptide therapeutics. Dendrimers have been shown to improve the solubility and stability of encapsulated peptides, thereby enhancing their therapeutic potential[31]. Table 1 summarizes the major nanocarrier platforms discussed for peptide delivery against vaginal infections, highlighting their structural properties, vaginal-specific advantages, and supporting preclinical data to provide a concise comparative overview that facilitates understanding of their therapeutic potential and application rationale.

While nanocarriers offer significant advantages for vaginal delivery of peptide-based therapeutics, challenges remain. The vaginal environment's dynamic nature, including its acidic pH and mucus turnover, can affect the stability and efficacy of these

delivery systems. Additionally, the potential for local irritation and the need for precise control over drug release kinetics are important considerations for the successful application of nanocarriers in this context. Further research and development are needed to optimize these systems for clinical use[8, 30].

STRATEGIES FOR VAGINAL TARGETING

The development of nanocarriers for peptide-based therapeutics against sexually transmitted vaginal infections involves several innovative strategies to enhance drug delivery and efficacy. These strategies include surface modifications, stimuli-responsive systems, and the combination with hydrogels or rings for sustained release. Each approach aims to overcome the unique challenges posed by the vaginal environment, such as mucus barriers and the need for prolonged drug residence time.

PEGylation involves coating nanoparticles with polyethylene glycol to facilitate their passage through the mucus layer by minimizing adhesive interactions with mucus components, thereby promoting a more uniform distribution and prolonged retention of drugs at mucosal surfaces while potentially decreasing direct uptake by epithelial cells due to reduced surface interactions[32]. In contrast, chitosan, a positively charged mucoadhesive polymer, is employed to increase the residence time of vaginal drug delivery systems by forming strong electrostatic interactions with the negatively charged mucin network, which helps maintain the therapeutic agent at the target site for an extended period and supports sustained local drug availability[33, 34].

pH-responsive nanoparticles are engineered to react to the acidic environment of vaginal mucus by shedding their PEG coating, which subsequently reveals a positively charged surface that can improve interaction with epithelial cells and enhance cellular uptake, thereby promoting localized drug release and better therapeutic outcomes[32]. Similarly, intravaginal rings incorporating pH-sensitive hydrogels can be designed to provide controlled, on-demand release of nanoparticle-based drugs in response to fluctuations in vaginal pH, enabling a more tailored and responsive treatment strategy that aligns drug delivery with physiological changes over time[35].

Hydrogels can encapsulate nanoparticles to provide sustained release of therapeutic agents, which enhances drug stability and bioavailability

Table 1. Overview of nanocarrier types for vaginal delivery of peptide therapeutics

Nanocarrier Type	Key Properties	Advantages for Vaginal Delivery	Preclinical Evidence	References
Liposomes	Lipid bilayers; encapsulate hydrophilic/hydrophobic peptides	Biocompatibility; mucoadhesion; stimuli-responsive release	Sustained antifungal activity in murine candidiasis models	[1, 27]
Polymeric NPs (PLGA, Chitosan)	Controlled release; enzyme protection	Mucoadhesion; tight junction opening; prolonged retention	Enhanced metronidazole efficacy vs. free drug in BV models	[29, 30]
Nanogels	Hydrophilic swelling networks	Mucus penetration; pH-responsive; high payload	Improved peptide stability and local bioavailability	[1, 8]
Micelles	Amphiphilic self-assembly	Small size for mucus diffusion; hydrophobic core	Efficient penetration in cervicovaginal mucus ex vivo	[8, 27]
Dendrimers	Branched structures; high surface functionality	Mucoadhesion/penetration; peptide solubility enhancement	Targeted delivery with reduced systemic exposure	[31]

and supports a prolonged therapeutic effect in the vaginal environment[33]. Intravaginal rings loaded with combinations of nanoparticles and hydrogels can deliver drugs continuously over extended periods, helping maintain relatively constant local drug concentrations, lowering dosing frequency, and potentially improving patient adherence[35]. Despite these advances in peptide-based vaginal delivery, important challenges persist, including achieving an optimal balance between mucus penetration and cellular uptake, ensuring that formulations remain acceptable and comfortable for patients, and establishing robust, standardized evaluation methods to reliably assess the safety and efficacy of these innovative systems in clinical use[36, 37].

PRECLINICAL EVIDENCE

The preclinical evidence for nanocarrier-peptide formulations against vaginal infections is promising, with various studies demonstrating their efficacy, biodistribution, and safety profiles in animal models. These formulations aim to enhance the therapeutic potential of peptide-based treatments by improving drug delivery, reducing dosing frequency, and minimizing systemic side effects. The following sections summarize key findings from in vivo and ex vivo studies on these formulations.

Nanocarrier-based systems markedly improve the efficacy of antimicrobial drugs for vaginal infections by enhancing drug retention, distribution, and potency compared with conventional formulations. In antifungal applications, encapsulating amphotericin B or miltefosine in nanocarriers such as alginate nanoparticles enables sustained local delivery, and miltefosine-loaded

alginate nanoparticles have shown that a single intravaginal dose can reduce fungal burden in murine candidiasis models to a level comparable to multiple doses of standard formulations[38]. For bacterial vaginosis, metronidazole-loaded chitosan-based nanoparticles significantly enhance antibacterial performance in vivo, achieving markedly greater reductions in bacterial counts than free metronidazole, consistent with reports of improved minimum inhibitory concentrations for metronidazole-loaded chitosan nanostructures[39]. In antiviral protection, mucus-penetrating nanoparticles carrying acyclovir monophosphate distribute more uniformly through cervicovaginal mucus and have been shown to protect a substantially higher proportion of mice against vaginal herpes simplex virus 2 challenge compared with soluble acyclovir at the same dose, underscoring their promise for prevention of sexually transmitted viral infections[40].

Nanocarrier-based vaginal formulations can improve retention and tissue coverage compared with conventional dosage forms. Prolonged retention has been reported for microemulsion-based systems, which can remain in the vaginal canal for extended periods and provide sustained antifungal activity, thereby lowering the need for frequent dosing in preclinical models [38]. Enhanced distribution is achieved with mucus-penetrating particles that spread uniformly over the vaginal epithelium and migrate into the deep vaginal folds, a feature considered critical for effective local drug delivery and sustained therapeutic levels [40].

Available preclinical data indicate that nanocarrier-based vaginal systems are generally biocompatible and can lower drug-

related toxicity compared with free drugs. Metronidazole-loaded chitosan nanoparticles have shown no significant cytotoxicity in standard cell assays and were considered safe in animal studies based on histopathological evaluation of vaginal tissues, supporting their suitability for local vaginal application[41]. Hybrid nanoparticles co-loaded with curcumin and benzydamine hydrochloride have been reported to markedly reduce cytotoxicity relative to the free, unencapsulated drugs, suggesting an improved safety profile for managing vulvovaginal candidiasis[42].

Despite these encouraging findings, moving from preclinical models to clinical practice remains challenging, because the human vaginal environment is highly complex, with diverse microbiota, variations in mucus and pH, and substantial patient-to-patient differences in adherence to intravaginal therapies. There is also the need to consider long-term effects, including potential shifts in the microbiome and the risk of antimicrobial resistance, which cannot be fully captured in short-term animal studies or in vitro tests. Ultimately, well-designed human clinical trials are essential to validate the safety, tolerability, and therapeutic benefit of these nanocarrier-peptide systems before they can be widely adopted for treating vaginal infections.

CONCLUSION, CHALLENGES AND FUTURE DIRECTIONS

The conclusion of a review paper on nanocarriers for peptide-based therapeutics against sexually transmitted vaginal infections should encapsulate the transformative potential of these systems while addressing the challenges and future directions. Nanocarrier-peptide systems offer promising solutions for improving therapeutic outcomes in vaginal STI management by enhancing drug delivery, stability, and bioavailability. However, several hurdles must be overcome to fully realize their potential in clinical settings. This section will explore these challenges and highlight emerging trends that could shape the future of this field.

Scalability, safety, and regulatory hurdles remain key obstacles to bringing vaginal nanocarrier systems into routine clinical use, despite strong preclinical promise. Large-scale, reproducible production of nanocarriers is difficult because traditional batch methods often yield polydisperse particles, high batch-to-batch variability, and elevated costs. Microfluidic and

electrospraying approaches improve control over size and composition and can be parallelized for higher throughput, but further engineering and process standardization are needed to ensure consistent quality and cost-effective industrial manufacturing[43, 44].

The small size and high surface reactivity of nanomaterials create a risk of unanticipated toxicities, including oxidative stress, inflammation, and off-target tissue accumulation, making comprehensive toxicity, immunogenicity, and biodistribution studies essential. Current safety assessments must consider long-term exposure, interaction with the vaginal microbiome and mucosa, and inter-individual variability, which requires extensive in vitro, in vivo, and ultimately human clinical testing before approval[44, 45].

Regulatory frameworks for nanomedicines are still evolving; agencies such as the FDA and EMA demand rigorous chemistry, manufacturing, and control data plus tailored toxicology packages because many existing standards were designed for non-nano drugs[44]. Translation to the clinic is further limited by biological barriers in the vaginal environment, including the mucus layer, epithelium, immune responses, and microbiota, which can restrict nanoparticle transport and lead to discrepancies between preclinical efficacy and human outcomes[31].

Smart nanocarrier-peptide systems for vaginal STIs aim to provide targeted and controlled local therapy, reducing systemic side effects and improving drug residence at the site of infection[45, 46]. These platforms can be engineered to respond to specific stimuli (for example, pH or enzymes), enabling on-demand payload release and enhancing therapeutic precision while limiting off-target effects[45, 47].

Future directions include combining nanocarriers with modalities such as gene editing or immunotherapy to overcome resistance, and using molecular modeling to design personalized peptide formulations tailored to individual patients. Their successful translation, however, depends on solving key challenges in large-scale manufacturing, long-term safety, and regulatory approval, which will require close collaboration between nanotechnology, pharmacology, and clinical experts.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this manuscript. All authors have disclosed any financial or personal relationships that could potentially influence or bias the work presented.

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