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ADVANCEMENTS IN VAGINAL DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

The review paper investigates innovative vaginal drug delivery systems aimed at overcoming the limitations of conventional treatments for vaginal infections such as bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis (TV). With over 70% of women affected by vaginal infections, the significance of the review lies in addressing the shortcomings of traditional therapies, which include low bioavailability, short residence time, and resistance issues, especially in recurrent and immunocompromised cases. The review evaluates a variety of advanced delivery systems—nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), hydrogels, microspheres, and films—highlighting their potential for localized treatment. Key findings indicate that these advanced systems significantly enhance drug retention and target infection sites effectively, with mucoadhesive systems prolonging residence time and offering sustained drug release. Notably, nanocarriers such as NLCs and liposomes demonstrate improved stability, bioavailability, and antimicrobial efficacy, while hydrogels and films facilitate controlled drug delivery with minimal systemic exposure. In conclusion, the review emphasizes the transformative potential of these novel vaginal drug delivery systems to enhance therapeutic efficacy and patient compliance by addressing the limitations of conventional therapies. Future research should focus on clinical validation and scalability to maximize their impact in real-world applications.

KEYWORDS: Vaginal drug delivery, Bacterial vaginosis, Nanocarriers, Solid lipid nanoparticles, Controlled drug release.

INTRODUCTION

Over 70% of women worldwide suffer from vaginal infections, which have a major negative influence on quality of life. The most prevalent kinds are trichomoniasis (TV), vulvovaginal candidiasis (VVC), and bacterial vaginosis (BV). BV affects about 29% of women of reproductive age globally and is caused by an imbalance in the vaginal microbiota, specifically a decrease in Lactobacillus species. It increases the risk of STIs and unfavorable pregnancy outcomes. Although it is not associated with serious health hazards, VVC, which is mostly caused by Candida albicans, affects up to 75% of women at least once and accounts for about 138 million cases annually. With a prevalence of 5.3% among women and an estimated 156 million new cases per year, TV, which is caused by Trichomonas vaginalis, is the most prevalent non-viral STI. TV can cause serious

reproductive health problems even though it is frequently asymptomatic.[1, 2]

Relationships and mental health may be impacted by these infections' symptoms. Accurate diagnosis and treatment are essential for effective management, and additional study is needed to address issues including bacteria resistance and biofilm formation. The efficacy of vaginal drug delivery devices in treating gynecological disorders such trichomoniasis (TV), vulvovaginal candidiasis (VVC), bacterial vaginosis (BV), and sexually transmitted infections (STIs) is drawing attention. These systems can produce both local and systemic therapeutic effects by avoiding first-pass metabolism. Because of the vagina's abundant blood supply, they are used for a variety of purposes, including as hormonal treatments, antimicrobials, and antifungals, which improve drug absorption. Reduced dosages and side effects are advantages over oral delivery, but there are drawbacks as well, like dilution by vaginal secretions. Factors like acidity and epithelium thickness, which change according on the menstrual cycle and state of health, must be taken into account in formulations. Numerous delivery techniques, including as gels and sophisticated nanotechnology systems, are being developed; nanocarriers, such as liposomes and nanoemulsions, provide targeted distribution and controlled release, supporting individualized treatments and microbicide-based infection prevention.[3, 4]

The aesthetic and functional aspects of vaginal drug delivery systems, such as melting at body temperature, being non-toxic and non-irritating, and not interfering with sexual activity, must be balanced. To extend drug retention, they should be odorless, stable in the vaginal pH range (3.5–4.9), and have good mucoadhesion. Recent developments combine pH-sensitive and temperature-sensitive formulations coupled with mucoadhesive and bioadhesive polymers to solve problems like quick medication removal. Targeted therapy is made possible by nanocarriers, which improve medication protection and mucosal penetration. When treating gynecological and reproductive health disorders, a variety of delivery options, such as inserts and emulsions, enable regulated drug release, enhancing patient compliance and overall user experience.[5, 6]

PHYSIOLOGICAL CONSIDERATIONS OF THE VAGINAL REGION

In the female reproductive system, the human vagina is a fibromuscular tubular organ with a somewhat S-shaped structure and a length of 6 to 12 cm. Three histological layers make up its wall: the muscularis, the middle layer, contains smooth muscle fibers for elasticity and contractility; the tunica adventitia, the outermost layer, is made up of areolar connective tissue for structural support; and the innermost layer is a non-secretory stratified squamous epithelium that provides protection. Rugae are transverse folds on the surface of the vaginal lumen that increase surface area and allow for stretching.[7, 8]

The vaginal environment is characterized by the absence of glands, adipose tissue, and hair follicles, with secretions primarily being transudates. The pH usually ranges from 3.8 to 4.5, maintained by Lactobacillus species that produce lactic acid from glycogen, crucial for protecting against infections. The vagina also facilitates menstrual flow, receives semen, and serves as part of the birth canal. Estrogen significantly impacts vaginal physiology by sustaining epithelial thickness and moisture, while the mucosal thickness varies throughout the menstrual cycle, regulated by sex hormones. Non-keratinized stratified squamous epithelium comprises about 28 cell layers early in the cycle, reducing to approximately 26 layers later, crucial for maintaining the vaginal environment. In pregnant women, vaginal pH shifts to 3.8–4.4, rising to 7.0–7.4 post-menopause.[9-11]

Extensive research shows that Lactobacillus species, which produce hydrogen peroxide and antibacterial chemicals to protect the reproductive system, make up the majority of the human vaginal microbiome. Nonetheless, a variety of different microbiota with low or missing Lactobacillus levels are present in many healthy women, suggesting several core microbiomes. Microbial makeup is greatly influenced by ethnicity; Asian and Caucasian women often have higher amounts of lactobacilli than Black and Hispanic women. Five vaginal microbial Community State Types (CSTs) have been identified based on the dominating Lactobacillus species. CST IV, which lacks Lactobacillus and has stringent anaerobes associated with bacterial vaginosis, is one of the CSTs. Throughout life, there are CST transitions, most notably from CST III to CST IV. Every species of Lactobacillus has a different set of skills. For example, Lactobacillus iners can adapt to different pH levels, but it is less effective against the rigorous anaerobes that are typical of CST IV.[12-14]

The most prevalent condition, bacterial vaginosis (BV), is marked by elevated levels of anaerobic bacteria such as Gardnerella vaginalis, an increase in vaginal pH, and a decrease in lactobacilli. Vaginal odor, discharge, and itching are among the symptoms; histological biofilm growth compromises mucosal defense. Candida albicans is the primary cause of vulvovaginal candidiasis (VVC), which manifests as vulvar erythema, thick white discharge, and itching due to hyphal penetration of the epithelium that compromises integrity. The most prevalent nonviral sexually transmitted infection, trichomoniasis (TV), is brought on by Trichomonas vaginalis, a protozoan that breaks down the epithelial barrier and causes frothy discharge and vaginal discomfort. These disorders all compromise the integrity of the epithelium, highlighting the necessity of a healthy, balanced vaginal microbiota and efficient treatment to avoid recurrence.[15, 16]

VAGINAL DRUG DELIVERY SYSTEMS

A vaginal drug delivery platform must address significant barriers, primarily the thick mucus layer of the vaginal epithelium, which traps therapeutic agents through electrostatic, hydrophobic, and hydrogen bonding interactions. This trapping leads to poor drug delivery as the mucus is naturally cleared, reducing particle residence time. Effective delivery systems should either avoid mucus adhesion or penetrate it quickly to deliver adequate therapeutic concentrations to the target site.[17, 18] Various novel drug delivery systems are illustrated, alongside their advantages and disadvantages. (Table 1)

Table 1: Various Novel Drug Delivery Systems Involved and their Advantages and Disadvantages.

Delivery System	Mechanism	Advantages	Disadvantages	Outcomes
Solid Lipid Nanoparticles	Matrix erosion and diffusion through a solid lipid matrix	Good skin compatibility, regulated release, low cytotoxicity, and physicochemical stability	Crystalline structure limits drug loading; lipid polymorphism risk	Enhanced therapeutic index (e.g., fluconazole, metronidazole); decreased recurrence; prolonged release for up to 24 hours
Microsponges	Diffusion through a porous polymeric matrix	High drug loading surface area, targeted and prolonged delivery, decreased irritation, and enhanced patient compliance	Insufficient for hydrophilic drug distribution; gels might be needed for mucosal application	Enhanced local retention and prolonged antifungal effect
Liposomes	Diffusion through phospholipid bilayers	Encapsulation of both hydrophilic and lipophilic drugs; enhanced mucosal penetration; biocompatibility	Low encapsulation of hydrophilic pharmaceuticals; unstable in bodily fluids; vulnerable to oxidative degradation	Improved antifungal efficacy; enhanced retention in mucosa
Nanocstructured Lipid Carriers	Controlled release via lipid matrix with liquid lipid dispersion	Longer mucosal residence, enhanced encapsulation effectiveness, increased drug solubilization, and prevention of drug expulsion	Potential lipid oxidation and a complicated formulation procedure	Effective against resistant strains; low systemic absorption; superior bioadhesion and antifungal action (e.g., amphotericin B, clotrimazole, luliconazole)
Polymeric Nano-particles	Polymer matrix biodegradation (PLGA, chitosan, etc.)	Biodegradability, controlled and targeted drug release, and adjustable surface charge for mucoadhesion	Stability, size, and charge fluctuation can all be impacted by polymer-drug interactions.	Efficient delivery of genes and siRNAs (like HSV-2); enhanced treatment response in animal models; decreased inflammation and infection
Dendrimers	Multivalent interaction or conjugation with therapeutic agents	High drug payload, enhanced cellular absorption, precise construction, and a surface that can be altered for targeting	Costly production; possible cytotoxicity in later generations	HIV-1 and HSV-2 inhibition (e.g., G2-S16); retained vaginal microbiota; appropriate for microbicidal application in human explants
Microspheres	Diffusion and polymer erosion (e.g., chitosan, alginate)	High encapsulation efficiency, extended release, customized release kinetics, and improved mucoadhesion	Particle aggregation danger; gel matrices or stabilizers may be necessary	Metronidazole and cefixime are delivered locally well; they adhere well to the vaginal epithelium and exhibit strong antibacterial and antifungal properties.
Hydrogels	Swelling-controlled diffusion and erosion	Strong mucoadhesion, enhanced comfort and retention, and thermosensitive and	Vaginal fluids decrease stability and increase the	Controlled release of substances such as curcumin, secnidazole, and subtilosin; improved wound healing and antibacterial action;

		pH-responsive behavior	likelihood of leakage.	decreased pathogen transmission
Vaginal Films	Hydration-induced disintegration and drug diffusion	Thin, discreet, portable; fast or sustained release options; good stability	Thin, discreet, portable; fast or sustained release options; good stability	Sustained anti-HIV activity; rapid disintegration with maintained vaginal flora
Vaginal Implants	Biodegradation-mediated sustained release	Long-acting delivery; reduced dosing frequency; high patient compliance potential	Invasive placement; risk of inflammation or foreign body sensation	Tissue-compatible; enhanced fibroblast adhesion; potential for treating pelvic floor disorders
Vaginal Rings	Diffusion or osmotic-controlled drug elution	Sustained release (weeks–months); high user adherence; customizable drug combinations	User acceptability concerns; ring expulsion risk	Proven effectiveness in preventing HIV (e.g., tenofovir, dapivirine); decreased VVC recurrence; and dual usage for STI prophylaxis and contraception

(a) Liposomes

The potential of liposomes, spherical vesicles with lipid bilayers, for medication administration is being investigated, especially for the treatment of vaginal infections. According to research, chitosan-decorated liposomes loaded with clotrimazole improve medication retention and fight biofilm in pregnant patients. Research shows that appropriate chitosan concentrations enhanced medication release and mucoadhesion. Deformable propylene glycol-containing liposomes (DPGLs) containing metronidazole or clotrimazole embedded in a Carbopol gel are another innovation that shows improved penetration and prolonged release. Mucoadhesive liposomes loaded with sertaconazole also show decreased penetration and delayed drug release, making them useful for treating vaginal candidiasis in vivo. Pro-liposomes and polyol dilution are two techniques for optimizing liposome production for vaginal therapy that demonstrated stability under vaginal simulation settings. Furthermore, resveratrol and polyphenol-containing formulations show excellent trapping efficiency and prolonged release with low toxicity. In the end, liposomes work well for targeted vaginal treatment; however, production and formulation stability issues still need to be resolved before clinical use.[19-21]

(b) Nanostructured lipid carriers

Comprising both liquid and solid lipids, nanostructured lipid carriers (NLCs) are sophisticated drug delivery devices that improve drug loading, stability, and controlled release. By guaranteeing extended contact with the mucosa and localized action, stabilized by surfactants, they increase the solubility and bioavailability of poorly soluble medications, making them especially useful for vaginal delivery. With good drug accumulation and safety characteristics, researchers have created NLCs for amphotericin B (AmB), which have shown notable success in treating vulvovaginal candidiasis and cutaneous leishmaniasis. By enabling the incorporation of different drugs and bioactive substances, NLCs improve solid lipid nanoparticle (SLN) technology. For upcoming clinical applications, scale-up, long-term stability, and human safety are still crucial factors.[22, 23]

(c) Microsponges

Usually composed of biodegradable materials and polymers like Eudragit, microsponges are porous particles used in drug delivery for controlled release of pharmaceuticals. Because of their bioadhesive qualities, they improve drug stability and targeting during vaginal delivery. According to research, miconazole-loaded microsponges in a gel formulation are more successful than conventional solutions for treating vaginal yeast infections. Fluconazole and oxiconazole nitrate microsponges, which similarly showed sustained release and better performance than current therapies, were used in other investigations. Furthermore, voriconazole-loaded nanosponges have demonstrated encouraging release and retention properties for vaginal infections. Overall, microsponges enhance drug delivery systems' stability, efficacy, and retention—especially in gynecological applications—confirming their potential to lower systemic adverse effects and improve therapeutic outcomes.[24-26]

(d) Dendrimers

Highly structured macromolecules called dendrimers allow for regulated medication loading and release. When combined with particular targeting ligands, they show promise for targeted vaginal medication delivery, increasing therapeutic efficacy while reducing off-target effects. Without changing the vaginal microbiome, the G2-S16 polyanionic carbosilane dendrimer has demonstrated effectiveness against HSV-2, preserving health even in the face of infection. In pregnant guinea pigs, a novel biodegradable hydrogel created by crosslinking dendrimers with polyethylene glycol promotes continuous amoxicillin release with no negative side effects. Additionally, dendrimers successfully elicit immunological responses against Chlamydia trachomatis by acting as carriers for peptide vaccines. Furthermore, dendrimers of the second and

third generations exhibit strong anti-HIV-2 action without causing any vaginal discomfort.[27-29]

(e) Films and inserts

Vaginal films and inserts are made to be comfortable for patients; the films are flexible and thin (50–200 µm thick), while the inserts are made to be easily inserted (2–3 cm length). To stick to the vaginal mucosa, both use mucoadhesive polymers like polyvinyl alcohol (PVA) or hydroxypropyl methylcellulose (HPMC). When in situ gelling systems come into touch with vaginal fluid, they create a gel depot due to variables like pH. Drug release and residence time are improved by this arrangement. A particular insert for chlorhexidine digluconate that uses chitosan/carboxymethylcellulose (CS/CMC) complexes has demonstrated excellent drug loading and antibacterial action against Escherichia coli and Candida albicans, suggesting efficacy in treating infections.[30, 31]

Researchers have developed a self-administered vaginal fast-dissolving insert (FDI) using freeze-drying to deliver griffithsin (GRFT) and carrageenan (CG) effectively. The lead formulation, FDI-024, consists of 4 mg GRFT and 15 mg CG, demonstrating rapid dissolution in under 60 seconds in simulated vaginal fluid, forming a viscous gel while retaining antiviral efficacy against HIV type 1 and HPV. Additionally, a mucoadhesive clotrimazole film for vaginal candidiasis was optimized using hydroxyl propyl cellulose and sodium alginate. This optimized film exhibited an in vitro disintegration time of 18 minutes, 99.83% drug content, and effective drug diffusion, while demonstrating antifungal activity against Candida albicans without disturbing beneficial vaginal flora.[32, 33]

(f) Microneedle arrays

By using tiny needles to increase the bioavailability of medications like vaccinations and antibacterial agents while lowering systemic exposure, microneedle arrays provide a minimally invasive way to deliver pharmaceuticals directly into the vaginal mucosa. Because these arrays are simple to operate, they improve patient compliance by facilitating the stability and controlled release of medicines. Estradiol valerate encapsulation in polylactic acid microneedles, which enables extended release over seven days with efficient penetration and durability, is an example of how biodegradable polymeric microneedle arrays (BPMNAs) have demonstrated potential for transdermal drug delivery. Furthermore, rilpivirine-loaded dissolving microarray patches (MAPs) for long-acting antiretroviral therapy show successful penetration and sustained plasma levels for up to 56 days, demonstrating efficacy in targeting HIV replicating sites. All things considered, these developments in microneedle technology improve vaginal drug delivery systems' effectiveness, safety, and patient autonomy.[34, 35]

(g) Electrospun nanofiber mats

Because of their special structural characteristics, electrospun nanofiber mats provide a novel method for vaginal medication delivery that improves therapeutic efficacy. These mats are made by electrospinning, which produces ultrafine fibers that enhance drug release and encapsulation. In order to treat diseases like bacterial vaginosis and vaginal candidiasis locally, they can be altered to incorporate mucoadhesive polymers, which help drugs adhere to the vaginal mucosa. Research shows that probiotics and antifungal drugs can be successfully delivered locally utilizing materials like polyvinyl alcohol for fluconazole and scaffolds that combine metronidazole with other drugs to fight bacterial vaginosis biofilms. Chitosan-based nanofibers for tenofovir administration have been investigated in other research, showing antiviral activity and safety. The results show that electrospun nanofibers can improve bioavailability, sustained release, and the efficacy of treating vaginal infections. Future developments are expected to improve drug loading methods and polymer combinations.[36]

REGULATORY CONSIDERATIONS AND CHALLENGES

Guidelines for vaginal products are ill-defined in many nations, and official compendia are devoid of information on quality control. FDA regulatory standards, including guidelines for vaginal contraceptives and antimicrobials related to disorders like gonorrhea and BV, should be evaluated prior to creating vaginal formulations. Along with the necessary reproductive studies at different stages, developers are required to submit nonclinical and pharmacological studies with an NDA. Multifunctional vaginal prevention technologies (MPT) provide regulatory challenges since they frequently require interaction with several regulatory agencies because they contain several physiologically active substances. Drug interactions must be thoroughly investigated, particularly for recently created or repurposed compounds. The clearance process for medicated vaginal MPTs is complicated because they are subject to additional regulatory supervision as both drug and medical device entities.[37]

Guidelines for vaginal medication delivery systems have been set by the FDA and EMA to guarantee quality, safety, and efficacy. For new drug applications (NDAs), the FDA's 21 CFR 310.505 specifies standards for preclinical research, clinical trials, labeling, and manufacturing controls. Clinical trial design, bioequivalency testing, and formulation design are all covered in detail in the Guidance for Industry. The Guideline on the Quality Requirements for Medicinal Products, which covers stability testing, analytical techniques, and good manufacturing practices (GMP), is part of the EMA guidelines. Furthermore, standards for generic vaginal drug delivery systems, including as bioequivalency testing and labeling, are outlined in the

Guideline on the Development and Registration of Generic Medicinal Products.

In toxicological studies, the FDA advises testing these medications at three distinct dose levels: a high dose that results in noticeable toxicity, a low dose that results in little to no harm, and an intermediate dose to determine the dose-response relationship. Pharmacokinetics is necessary because of the mucosal membrane's high permeability. Furthermore, all goods should be tested for rabbit irritation, reproductive toxicity, carcinogenicity, and genotoxicity (e.g., AMES test, in vitro mouse TC lymphoma assay, mouse micronucleus test).[38]

PERSONALIZED MEDICINE APPROACHES

Personalized medicine focuses on customizing treatment based on individual patient characteristics, including genetics and lifestyle. In vaginal drug delivery, personalized approaches involve developing drug formulations tailored to factors like vaginal pH and microbiota. A study highlighted the necessity for individualized dosages and delivery methods to minimize adverse effects from hormonal therapies. Advances in 3D printing enable the creation of patient-specific implants, designed with factors like anatomy and hormone release schedules in mind. Regulatory bodies are standardizing guidelines for personalized drug delivery devices produced, particularly in point-of-care settings. This integration promises to transform women's healthcare by improving treatment outcomes and reducing costs associated with vaginal infections and reproductive health issues.[39, 40]

PRODUCTION AND COMMERCIAL CHALLENGES

Significant therapeutic potential is revealed by research on enhanced vaginal drug delivery systems, however commercialization obstacles still exist. One of the main challenges is scalability, since laboratory formulations frequently have issues with cost, stability, and repeatability in large-scale production. Complexity and cost are increased by the need for specialized equipment and stringent regulatory compliance. Processes are made more difficult by the need to achieve batch consistency, particularly when using different methods for mucoadhesives or nanocarriers. Furthermore, elements like patient acceptability, long-term stability, and ease of handling are crucial for industry adoption and must be taken into account early in development to improve clinical translation and financial feasibility.[41, 42]

Real-life examples such as the NuvaRing® and Crinone® illustrate the challenges of developing vaginal drug delivery systems. The NuvaRing® achieved market success through optimized polymer extrusion and extensive stability assessments, while Crinone® enhanced patient compliance with prefilled applicators, despite increased production costs. Efforts to introduce microbicide gels for HIV prevention faced hurdles including manufacturing difficulties and user adherence issues. Overall, the potential of innovative vaginal formulations is tempered by concerns over scalability, manufacturing complexities, and regulatory compliance. Multidisciplinary collaboration will be essential to transition these innovations from labs to practical use.[43]

CONCLUSION

The physiological aspects of the vaginal environment that influence design are highlighted in this overview of new drug delivery systems (VDDS) for vaginal infections. It covers a variety of systems, including as controlled release technologies, mucoadhesives, nanoparticles, and devices that target diseases like trichomoniasis and bacterial vaginosis. More reliable mechanisms are required to penetrate the vaginal mucosa and guarantee prolonged medication release, even with current products. Given the limitations of present animal studies, future research should concentrate on filling up gaps in translational models and drug release techniques. To evaluate the safety and effectiveness of these improvements, clinical trials are essential. To enhance patient outcomes and advance therapies for women's health, industry, healthcare providers, and researchers must work together.

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