RESEARCH PAPER

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR VAGINAL CANDIDIASIS: A PHARMACEUTICS PERSPECTIVE

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ABSTRACT
Vulvovaginal candidiasis (VVC) is the most prevalent fungal infection among women globally. Although *Candida albicans* is the primary pathogen, non-albicans Candida species are becoming increasingly associated with recurrent and drug-resistant infections. Conventional antifungal medications often exhibit limited clinical efficacy due to factors such as poor drug solubility, insufficient mucosal penetration, brief residence time in the vagina, and the necessity for frequent dosing. Additionally, the development of antifungal resistance linked to biofilm formation complicates treatment. These challenges emphasize the necessity of enhanced vaginal drug delivery methods. This study outlines the pathophysiology of vaginal drug delivery, addressing aspects such as mucus turnover, acidic vaginal pH, and epithelial permeability barriers, along with associated risk factors. It emphasizes the potential of nanotechnology-based approaches, including liposomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polymeric nanoparticles, to improve antifungal therapy. Specifically, mucoadhesive systems and nano-gel formulations are crucial for enhancing vaginal retention, enabling controlled drug release, and achieving targeted therapeutic effects. The review further explores how nanocarriers can combat antimicrobial resistance through biofilm penetration, prolonged drug release, targeted delivery, and efflux pump inhibition. Additionally, it highlights essential evaluation parameters for optimizing nanoformulations. The future prospects discussed include promising emerging strategies, such as stimuli-responsive systems, microbiome-based therapeutics, personalized delivery, and smart gels. Overall, nanotechnology-based vaginal delivery systems have the potential to enhance therapeutic efficacy, reduce recurrence rates, and improve patient compliance in VVC treatment.

Keywords: Vulvovaginal candidiasis; Nanotechnology; Vaginal drug delivery; Nano formulation; and Antifungal therapy
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INTRODUCTION

Vulvovaginal candidiasis (VVC) is a common mucosal fungal infection in the female reproductive tract, that causes itching, discharge, irritation and pain. It is usually caused by opportunistic overgrowth of Candida species, which are often present as commensals in the vaginal microbiome[1].
Worldwide, VVC occurs in nearly three-quarters of women once in their lives, and in some cases, frequent infection occurs, presenting a significant health concern to women[2].
Candida albicans is the most common cause of infection (approximately 85-90%), but non-albicans species such as *C. glabrata, C. tropicalis*, and *C. krusei* are also associated with recurring and drug resistant infections[3].
Although antifungal therapies are available, the management of VVC is still difficult because of a multitude of limitations related to traditional treatment modalities, including poor drug retention, inadequate mucosal penetration, frequent dosing schedules, and development of antifungal resistance. The dynamic vaginal environment, biofilm formation, and poor absorption of medication, eventually leads to treatment failure and recurrence[4]. This makes the development of better drug delivery systems, which are capable of enhancing drug retention, targeting, prolonged release and overcoming resistance mechanisms necessary. This review aims to critically examine the current advances in nanoformulation-based methods and vaginal drug delivery systems to successfully treat vulvovaginal candidiasis, with special focus on improving therapeutic efficacy and patient outcomes[5].

1. OVERVIEW OF VAGINAL CANDIDIASIS

Fungal infections affect billions of people worldwide and are estimated to be the cause of 1.5 million deaths each year, making them a significant but underappreciated global health burden. Advances in medical care have led to a dramatic increase in systemic mycoses since the mid-twentieth century. These opportunistic pathogens exploit the compromised host defences, and the severity of illness is largely dependent on both fungal virulence and the host's immunological status. Invasive fungal infections are a substantial public health burden, with fatality rates ranging from 30 to 90 percent[6].
Vaginal candidiasis, or vulvovaginal candidiasis (VVC), is a frequent fungal infection of the female

genital system caused mostly by yeasts of the Candida species, specifically *Candida albicans*. This is the most common cause of vaginitis, second only to bacterial vaginosis in many clinical settings and it contributes significantly to gynaecological morbidity in reproductive - aged women globally[7].

Vaginal candidiasis is a widespread disease that affects roughly three out of every four women throughout their lives[8]. Seventy - five percent of women have experienced a vaginal yeast infection at least once during their adult lifetimes. Furthermore, recurrent VVC affects roughly 8% of women worldwide[9].

Despite its high prevalence, vulvovaginal candidiasis incidence is difficult to estimate due to underreporting, widespread self-medication, and diagnostic technique heterogeneity. However, it is commonly acknowledged as the second most common cause of vaginitis, considerably contributing to gynaecological morbidity and healthcare utilisation[10].

1.1 Etiology of Vaginal Candidiasis

Vulvovaginal candidiasis (VVC) is mainly due to excessive growth of Candida species, which are normal components of the vaginal microbiota. *Candida albicans* is linked to recurrent or complicated infections, with non-albicans Candida species such as *Candida glabrata, Candida tropicalis*, and *Candida krusei*. Infection is a condition that arises when the relationship between the growth of the fungi and the host's defence is disturbed[11].

Candida species are opportunistic pathogens, meaning that they are harmless in normal conditions but become pathogenic in the case of changes in host immunity or environmental balance. They are virulent due to their ability to adhere to epithelial cells, form biofilms, switch phenotype, and secrete hydrolytic enzymes. It is important to note that the switch of C. albicans from yeast to hypha is essential for tissue invasion[12].

Lactobacillus species are predominant in healthy vaginal microbiota and maintain an acidic pH (3.84.5) and prevent the growth of pathogens. An imbalance (dysbiosis) of this balance, often caused by using antibiotics or disease, causes a reduction in Lactobacillus and increases the vaginal pH, which favours Candida overgrowth[13].

VVC is mainly endogenous and it is caused by Candida which is present in the gastrointestinal or the genitourinary tract. Exogenous transmission occurs infrequently and can be through medical procedures or contact, but VVC is not perceived as a sexually transmitted infection[14].

Hormonal influences, especially high levels of estrogen (e.g. during pregnancy or in the presence of contraceptives) increase susceptibility by increasing glycogen stores in vaginal cells and modulating local immune responses, thus permitting fungal growth[15].

1.2 Causative Organism: *Candida albicans*

The primary cause of vulvovaginal candidiasis (VVC) and a normal commensal of the oral, gastrointestinal, and vaginal mucosa is *Candida albicans*. The condition becomes pathogenic when the microbiome is imbalanced, there is a change in hormones or immunosuppression[16].

It is a dimorphic, opportunistic fungus which is able to change between yeast and hyphae forms, which helps it to invade tissues. It also develops biofilms, which enhance resistance to antifungal treatment[17].

Candida species have been listed by the World Health Organization as important pathogens. Even though C. albicans is the most common, non-albicans species, such as C. glabrata and C. krusei, are being increasingly linked to resistant infections[18].

1.3 Major Risk Factors Associated with Vulvovaginal Candidiasis[19-21]

TABLE 1

1.4 Pathophysiology and Virulence Factors

Lactobacillus spp. predominate the vaginal microbiota, which has an acidic pH, restricting the growth of pathogens. Candida can also persist as a commensal, although disruption of microbiomes (e.g., antibiotics, hormonal changes) favours overgrowth and symptomatic VVC[22].

Pathogenesis is proliferated by *Candida albicans* virulence factors, especially its capability to change between its yeast and hyphal forms, which facilitates tissue invasion. Additional factors, such as candidalysin and secreted enzymes contribute to epithelial damage and persistence[23].

Host response, predominantly that of polymorphonuclear neutrophils (PMNs), is not usually effective because of fungal immune evasion. This causes increased inflammation without sufficient clearance of fungi, which is one of the main characteristics of VVC[24].

Candida species that do not belong to the albicans group cause weaker immune responses and result in mild and persistent infections[25,26].

1.5 Clinical Manifestations of Vaginal Candidiasis[27,28]

FIGURE 1

2. LIMITATIONS OF CONVENTIONAL THERAPY[29-31]

TABLE 2

3. CHALLENGES IN VAGINAL DRUG DELIVERY

Localised action and avoidance of first-pass metabolism are the positive properties of vaginal drug distribution, but its efficiency is limited by numerous physiological and formulation-related challenges[32].

The rapid formulation clearance and short residence time are due to the dynamic vaginal environment, which is characterised by mucus turnover and self-

cleansing activity. Moreover, the mucus barrier prevents diffusion of medication by entrapping particles within its viscoelastic network, preventing epithelial infiltration[33].

Variable drug performance is due to the acidic vaginal pH (3.5-4.5), which may affect the drug solubility and stability, and to the alterations in physiology due to hormonal changes or infections. Having enzyme activity in vaginal secretions leads to the degradation of medications and reduced bioavailability[34].

Stratified vaginal epithelium also restricts drug penetration by keeping out high molecular weight and low lipophilic medicines. Hormonal fluctuations may influence the nature of mucus and the thickness of the epithelium, which affects the absorption of drugs[35].

Traditional formulations often exhibit poor mucoadhesive properties, leading to the early loss of the drug and the need to use it frequently, which is undesirable for patient adherence. Patient-related factors that affect treatment adherence include discomfort and cultural barriers[36].

Then, the growth of Candida biofilms significantly reduces the diffusion of antifungals and increases the resistance to treatment and recurrent infections. These challenges require the development of sophisticated delivery systems like mucoadhesive platforms and nanocarriers to improve medication retention and therapeutic efficacy[37].

FIGURE 2

4. NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR VAGINAL CANDIDIASIS

TABLE 3 [38-45]

5. MUCOADHESIVE SYSTEMS IN VAGINAL DRUG DELIVERY

5.1 Mucoadhesion

Mucoadhesion is a characteristic of a material, usually a hydrophilic polymer, to adhere to the mucus layer covering epithelial tissues, including the vaginal mucosa. It is involved in polymer-mucin interactions, for example, hydrogen bonding, electrostatic attraction and physical chain interpenetration. The vaginal mucosal surface has a negatively charged glycoprotein network that interacts with functional groups on the polymers, such as amino, carboxyl and hydroxyl groups. These interactions improve the localisation of the medicines and their retention by creating a powerful sticky surface[46].

5.2 Importance in Vaginal Drug Delivery

Vaginal route has the following advantages: it avoids first-pass metabolism, large absorptive surface area, and localised therapy; however, it is limited by rapid clearance by a mucus turnover and vaginal fluid leakage[47].

Mucoadhesive systems are necessary since they:

- Extending the duration of drug residency at the site of action
- Increasing the concentration and bioavailability of drugs locally
- Lowering the frequency of doses and systemic adverse effects

According to recent research, mucoadhesive formulations greatly enhance tissue absorption and medication retention, improving treatment outcomes for vaginal infections and other ailments[48].

5.3 Types of Mucoadhesive Vaginal Dosage Forms[49,50]

FIGURE 3

5.4 Mechanism: How Mucoadhesive Systems Increase Residence Time

Mechanism: The way Mucoadhesive Systems raise Residence Time. Mucoadhesive techniques extend the vaginal residency period through several complementary mechanisms:

- Polymer hydration and swelling lead to an increase in surface area and close contact.
- Mechanical anchoring through chain interpenetration with the mucin network
- Strong adhesion is the result of hydrogen bonding and electrostatic interactions.
- Enhancement of viscosity → decreases clearance and leaks

Secondly, the environmental factors such as vaginal pH influence the polymer adhesion and swelling that influence the medication release and retention. Altogether, these mechanisms would help the mucoadhesive systems to resist the rapid vaginal clearance to ensure long-term drug supply and improved treatment outcomes[51].

6. NANOCARRIER-INTEGRATED GEL SYSTEMS (NANO–GEL SYSTEMS)

The hybrid nanocarriers and gel-based drug delivery systems, also referred to as the nano-gel systems, are a novel form of vaginal drug delivery. The non-invasive nature of nanocarriers and mucoadhesive and retentive properties of gels overcome the major drawbacks of nanocarriers and gels in the vaginal environment, namely rapid clearance of nanocarriers, low bioavailability and variability in drug distribution in the vaginal environment. Nano-gel systems are particularly promising in the treatment of vulvovaginal candidiasis (VVC) and require prolonged residence time and localised drug activity for therapeutic success[52].

6.1 Niosomal gels

The niosomal gels are prepared by dispersing niosomes (non-ionic surfactant-based vesicles) in a gel base such as Carbopol or HPMC. These vesicles can carry not only hydrophilic but also lipophilic medicine, and this enhances the stability of medication and the delivery efficacy. Niosomes can target and deliver drugs in a controlled and sustained way, whereas the gel foundation allows the drug to be held at the site of delivery. The mixture significantly improves medicine absorption through the vaginal mucosa while minimizing systemic exposure[53].

According to recent studies, niosomal gels have

- Increased entrapment efficiency.
- Improved permeability and bioavailability
- Sustained drug release throughout time

Moreover, niosomes are biocompatible and biodegradable, and are more stable than liposomes, thus making them suitable to be used in the vagina[54].

6.2 Liposomal gels

The liposomal gels are formulated by incorporating phospholipid-based vesicles (liposomes) into a gel matrix. Liposomes are similar to biological membranes, and it is possible to administer medication with the help of liposomes in the vagina at the level of epithelial layers[55].

When liposomes are added to gels, they exhibit:

- Improved medication retention in vaginal tissues.
- Reduced drug degradation.
- Improved localised therapeutic impact.

The gel matrix prevents leakage and early removal of liposomes, and deep penetration and long retention of drugs in the deep mucosal layers. This two-fold strategy has been of great help in improving the outcome of therapy in vaginal infections[56].

Nevertheless, liposomal gels can be associated with certain drawbacks, i.e. the high costs of production and the problem of stability, which has provoked a certain revival of interest in other systems, e.g. niosomal gels[57].

6.3 Nanoemulsion-based gels (nanoemulgels)

Among the most rigorously studied technologies of nano-gel as vaginal delivery technologies are Nanoemulsion-based gels (nanoemulgels). These techniques involve a combination of the positive properties of nanotechnology and semisolid dosage forms by using oil-in-water nanoemulsions dispersed in a gel matrix.

Nanoemulgels provide:

- Improved solubility of poorly water-soluble antifungal medicines
- Enhanced penetration of mucosal barriers
- Controlled and sustained drug release.

Recent research indicates that nanoemulsion gels dramatically improve vaginal drug delivery by increasing drug distribution, retention, and therapeutic efficacy while maintaining patient safety and compliance. Moreover, nanoemulgels overcome significant vagina delivery challenges, such as rapid washout and limited dwell time and would therefore be suitable in the antifungal treatment[58].

6.4 ADVANTAGES OF NANO - GEL SYSTEMS

6.4.1 Sustained Drug Release

Regulated and prolonged release of drugs can be achieved by using nano-gel technologies, which help to maintain therapeutic drug concentrations over time and reduce dose frequency[59].

6.4.2 Improved Vaginal Retention

The gel base facilitates mucoadhesion, leading to increased residence time in the site of infection and reduced loss of medication due to vaginal fluid turnover[60].

6.4.3 Reduced Drug Leakage

By encapsulating the pharmaceuticals in nanocarriers, the premature leakage and degradation of the pharmaceuticals is minimised, which enables the pharmaceuticals to be delivered in a focused and effective manner[61].

6.4.4 Enhanced Bioavailability

Nanocarriers enhance the solubility of the medication, its stability and penetration, leading to the increased bioavailability and clinical efficacy[62].

6.4.5 Targeted and Localized Action

These devices are applied to the area of infection, delivering medications directly to the target site, reducing the systemic side effects and enhancing patient compliance[63].

7. EVALUATION PARAMETERS OF NANO FORMULATIONS

TABLE 4 [64-70]

FIGURE 4

8. ROLE OF NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS IN OVERCOMING ANTIMICROBIAL RESISTANCE

Drug delivery systems based on nanotechnology have become one of the applicable methods of fighting antimicrobial resistance, particularly in biofilm-related diseases. Their distinct physicochemical qualities, which include nanoscale size, surface tunability, and controlled drug release, allow them to address significant constraints of traditional therapies such as poor penetration, subtherapeutic drug levels, and non-specific dispersion.

8.1 Biofilm Penetration Enhancement

Mechanism: Nanoscale size and surface modification enable diffusion through extracellular polymeric substance (EPS) matrix; enzyme-functionalized systems degrade biofilm components

Impact on Antimicrobial Resistance: Improves drug access to embedded pathogens and enhances bacterial eradication[71].

8.2 Sustained and Controlled Drug Release

Mechanism: Controlled release kinetics maintain prolonged therapeutic drug concentrations

Impact on Antimicrobial Resistance: Prevents subtherapeutic exposure and reduces resistance development[72].

8.3 Targeted Drug Delivery

Mechanism: Surface functionalization with ligands (antibodies, peptides) enables site-specific delivery

Impact on Antimicrobial Resistance: Enhances local drug accumulation and minimizes off target toxicity[73].

8.4 Reduced Dosing Frequency

Mechanism: Prolonged drug release reduces need for repeated administration

Impact on Antimicrobial Resistance: Improves patient compliance and prevents incomplete therapy-associated resistance.

8.5 High Local Drug Concentration

Mechanism: Nanocarriers accumulate at infection sites and within biofilms

Impact on Antimicrobial Resistance: Enhances bactericidal activity and overcomes drug tolerance[74].

8.6 Efflux Pump Inhibition

Mechanism: Nanoparticles bypass or inhibit microbial efflux pumps, enhancing intracellular drug retention

Impact on Antimicrobial Resistance: Reduces multidrug resistance and improves antibiotic efficacy[75].

8.7 Stimuli-Responsive Drug Release

Mechanism: Drug release triggered by pH, enzymes, or redox conditions specific to infection sites

Impact on Antimicrobial Resistance: Enables precise drug delivery and reduces systemic exposure[76].

8.8 Multifunctional / Combination Therapy

Mechanism: Co-delivery of multiple agents (antibiotics, enzymes, peptides) or ROS generation

Impact on Antimicrobial Resistance: Produces synergistic effects and targets multiple resistance pathways[77].

DELIVERY - FOCUSED ADVANCES IN VAGINAL THERAPEUTICS[78-80]

TABLE 5

CONCLUSION

Vulvovaginal candidiasis remains a prevalent and recurrent infection, presenting significant therapeutic challenges due to the limitations of traditional antifungal treatments and the rising incidence of drug-resistant Candida species. As previously mentioned in this review, issues such as low drug retention, inadequate drug penetration, biofilm formation, and patient non-compliance severely undermine therapeutic outcomes. Nanotechnology-based drug delivery systems have emerged as a promising solution, offering enhanced drug solubility, controlled and sustained release, improved mucosal penetration, and targeted delivery to infection sites. Mucoadhesive formulations and nano-gel systems facilitate better vaginal retention and therapeutic efficacy by overcoming key physiological barriers in the vaginal environment. Additionally, these peptides possess the ability to bypass antimicrobial resistance mechanisms, such as biofilm disruption and efflux pump inhibition, positioning them as next-generation antifungal therapies. Recent advancements in areas like stimuli-responsive systems, microbiome-based drugs, and smart gels have expanded the potential for developing personalized, highly effective treatment plans. Although preclinical and experimental findings are encouraging, several challenges remain, including large-scale manufacturing, long-term safety, regulatory approval, and clinical translation. Ultimately, the integration of nanotechnology with vaginal drug delivery systems presents a promising and evolving platform for effectively treating vulvovaginal candidiasis. Ongoing research and clinical validation are essential to transform these advanced technologies into practical therapeutic solutions that could significantly reduce recurrence rates and enhance the quality of life for affected women.

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Formulations)

Parameter	Definition / Principle	Methodology / Instrumentation	Desired Range / Criteria	Significance in Drug Delivery
Particle Size[64]	Average diameter of nanoparticles influencing biological interaction and transport	Dynamic Light Scattering (DLS), TEM, SEM	10–200 nm (ideal for nano drug delivery)	Controls cellular uptake, biodistribution, permeation, and release kinetics
Polydispersity Index (PDI)[65]	Measure of particle size distribution uniformity	DLS	< 0.3 (monodisperse system)	Ensures formulation homogeneity, reproducibility, and stability
Zeta Potential[66]	Surface charge indicating electrostatic stability of nanoparticles	Zeta analyzer (Electrophoretic Light Scattering)	±30 mV (stable system)	Prevents aggregation, improves stability and mucoadhesion
Entrapment Efficiency (EE%)[67]	Percentage of drug encapsulated within nanocarrier	Centrifugation, ultrafiltration, spectrophotometry	>80% (optimal)	Enhances drug loading, reduces dose frequency, improves efficacy
In Vitro Drug Release[68]	Rate and extent of drug release from nanoformulation	Dialysis bag diffusion, USP dissolution apparatus	Sustained / controlled release profile	Maintains therapeutic concentration, reduces dosing frequency

Ex Vivo Permeation[69]	Drug permeation across biological membranes	Franz diffusion cell using animal/human tissue	Higher flux and permeability coefficient	Evaluates real-time absorption and mucosal penetration
Stability Studies[70]	Assessment of physical and chemical stability over time	ICH guidelines (temperature, humidity studies)	Minimal variation in size, PDI, EE%	Ensures shelf-life, safety, and formulation integrity

TABLE 5 (Delivery - Focused Advances in Vaginal Therapeutics)

Delivery Strategy	Mechanism of Action	Key Advantages	Representative Findings (Recent Studies)
Stimuli-Responsive Systems	Respond to vaginal microenvironment triggers (pH, enzymes, temperature) for controlled, on-demand drug release	Site-specific delivery, reduced systemic exposure, programmable release kinetics	Infection-triggered systems show enhanced antifungal release; dual-responsive systems improve targeting precision
Targeted Delivery Systems	Surface engineering enhances mucus penetration and selective binding to epithelial cells or pathogens	Improved drug localisation, enhanced biofilm penetration, reduced dosing frequency	PEGylated nanoparticles improve cervicovaginal mucus transport; biofilm-targeting systems enhance antifungal efficacy
Microbiome-Based Delivery	Utilise microbial enzymes/metabolites or restore Lactobacillus dominance to modulate drug release and vaginal health	Restoration of vaginal homeostasis, reduced recurrence, personalised therapeutic approach	Systems leveraging microbial cues show improved dysbiosis correction and targeted drug release
Combination Therapy (Drug + Probiotic)	Simultaneous pathogen eradication and microbiota restoration via synergistic mechanisms	Reduced recurrence rates, enhanced therapeutic efficacy, improved vaginal ecosystem balance	Nano-encapsulation improves probiotic viability; co-delivery systems outperform monotherapy in infection control
Smart Gels (Thermo-/pH-Sensitive Systems)	Sol–gel transition at vaginal temperature or infection-specific pH, enabling sustained drug release and retention	Prolonged residence time, improved patient compliance, reduced leakage, sustained drug levels	Thermogels show improved retention and bioavailability; nanocomposite gels enhance controlled release

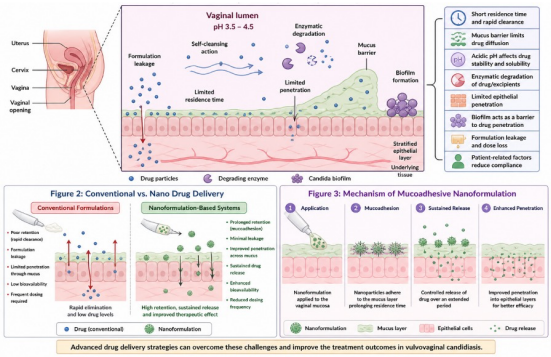
FIGURES

FIGURE 1: Clinical Manifestations of Vaginal Candidiasis

FIGURE 2: Challenges In Vaginal Drug Delivery

FIGURE 3: Types of Mucoadhesive Vaginal Dosage Forms

FIGURE 4: Evaluation Parameters of Nano Formulations



Advanced drug delivery strategies can overcome these challenges and improve the treatment outcomes in vulvovaginal candidiasis.