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Review

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OXFORD

Exploring the potential of vaginal drug delivery: innovations, efficacy, and therapeutic prospects

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Abstract

Vaginal drug delivery has gained significant interest due to its numerous advantages, such as good blood flow, bypassing the first-pass effect, low systemic side effects, and potential for sustained release of pharmaceuticals. Initially targeting contraception and local effects from antibacterial, antifungal, and antiviral agents, recent advancements have broadened its scope. Notably, microbicide formulations showed promise against sexually transmitted diseases, offering superior protection and effective hormone therapies due to the vagina's large surface area and high permeability. The main agents used in vaginal delivery include contraceptives, prostaglandins, steroids, and antimicrobial substances, administered through tablets, suppositories, ointments, gels, creams, and vaginal rings. However, challenges such as slow dissolution and short residence time necessitate novel delivery systems. Mucoadhesive polymers are particularly valuable for enhancing drug absorption and extending treatment options. Comparative studies indicate that vaginal absorption of drugs like human growth hormone and insulin surpasses other parenteral routes. The development of standardized *in vitro* and *in vivo* testing methods remains crucial due to the diverse drug systems. While vaginal drug delivery offers benefits, such as high vascularization, low enzymatic activity, and increased bioavailability, it also faces drawbacks, including limited drug compatibility, sensitivity to vaginal pH, patient compliance issues, and potential local irritation. This review aims to elucidate the pathway, propose standardized methods for specific therapeutic areas, and highlight novel formulations like hydrogels and lipid nanoparticles for treating various diseases.

Keywords: bacterial infection; cervical cancer; human immunodeficiency virus; therapy; vaginal drug delivery

Introduction

Vaginal drug delivery has garnered significant interest over the centuries due to its unique physiological and pharmacological advantages. This route bypasses the first-pass metabolism, ensuring good blood flow, low systemic side effects, and the potential for sustained drug release. Initially focused on contraception and local treatments for bacterial, fungal, and viral infections, the scope of vaginal drug delivery has expanded, with microbicide-based formulations showing promise against sexually transmitted diseases like HIV. Compared to traditional prevention methods, these formulations offer superior protection and systemic effects due to the large surface area, permeability, and high blood supply of the vagina, making it effective for hormone replacement therapies and contraception [1, 2]. It is of great importance that vaginal drug delivery systems ensure their safety, efficacy, and patient acceptability. Physicochemical properties, such as particle size, pH, viscosity, and drug solubility, play a key role in mucosal penetration, retention, and controlled drug release. Mucoadhesion and permeability are crucial for sustained local or systemic absorption, while an optimal release profile minimizes dosing frequency. Biocompatibility is another critical factor, as formulations must be nontoxic, nonirritating, and microbiome-friendly to maintain vaginal health. Additionally, microbiological quality must be ensured through sterility or appropriate preservative systems, particularly in multi-dose formulations. Stability is also essential, as both physical and chemical properties must remain consistent throughout the product's shelf life. Lastly, patient acceptability factors, such as ease of application and minimal leakage, are important for adherence to treatment and overall user experience [3–5].

The primary agents used in vaginal delivery include contraceptives, prostaglandins, steroids, and antimicrobial substances. These agents are delivered through various forms, such as tablets, suppositories, ointments, gels, creams, and vaginal rings. Despite their efficacy, these formulations often suffer from slow dissolution and short residence times, necessitating the development of novel delivery systems. The vaginal mucosal layer's mucoadhesive properties are exploited using mucoadhesive polymers to enhance systemic delivery and expand treatment possibilities. Enhanced absorption of pharmacological molecules like human growth hormone, insulin, and steroids has been observed when administered vaginally compared to other parenteral routes [6, 7].

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An interesting property of the organ under consideration is the mucosal layer that it presents, which makes the mucoadhesiveness of formulation an important property. Hence, mucoadhesive polymers are commonly used to establish a modification of the dosage form and achieve a systemic delivery through the vaginal mucosa and, thus, extend the range of possible treatments to be performed by this administration route. When comparing the vaginal absorption of pharmacological molecules, such as human growth hormone, insulin, or steroids, with other parenteral routes, an enhanced absorption can be observed [8, 9]. Furthermore, *in vitro* and *in vivo* testing methodologies play an important role in the progress of the vaginal drug delivery. Nevertheless, the wide variety of drug systems results in the difficult development of standardized testing methods [10].

Favourable properties of the vaginal administration route can be summarized as effective for orally inactive drugs, high vascularization, low enzymatic activity, prolonged release, increased bioavailability, the avoidance of the first-pass metabolism, quick onset of action, possible self-medication, low systemic side effects, and a lower dose is used in comparison to the oral route of administration. Nonetheless, only few drugs can be administered, the sensitivity of the pharmaceutical agent to vaginal pH is an important factor to consider, change in drug absorption as well as gender-specific, patient incompliance, and local irritation of drugs are some drawbacks that are under scope [11–14].

This review aims to elucidate the vaginal drug delivery pathway and propose modifications to standardized methods for specific therapeutic areas. It also highlights novel drug formulations, such as hydrogels, polymer-based nanocarriers, lipid nanoparticles, and liquid crystals, and their application in treating various diseases. Nanocarriers offer significant advantages over conventional carriers for vaginal drug delivery, primarily due to their ability to enhance drug solubility, prolong retention time, and provide controlled release. Their nanoscale size allows for better mucosal penetration and interaction with vaginal epithelial cells, improving bioavailability. Additionally, nanocarriers can be engineered for targeted delivery, reducing systemic absorption and minimizing side effects. In contrast, conventional carriers, such as gels or creams, often exhibit rapid drug release and limited retention, leading to frequent reapplication and variable therapeutic outcomes. While traditional formulations remain widely used due to their ease of production and cost-effectiveness, nanocarriers represent a promising alternative for achieving more efficient and patient-friendly vaginal drug delivery [15, 16]. Despite its potential, many aspects of vaginal drug delivery require further research and development to realize its full potential.

Background

Despite the numerous advantages of vaginal drug delivery and its potential for innovative formulations, several challenges remain. Key factors, such as bioadhesion, drug distribution, controlled release, and retention time, play a crucial role in the effectiveness of these delivery systems. While advancements in mucoadhesive polymers and nanocarrier-based formulations have addressed some of these limitations, further improvements are necessary to optimize drug absorption, patient compliance, and therapeutic outcomes. Understanding the strengths and drawbacks of existing vaginal administration systems is essential for guiding future research and innovation in this field.

Many advantages can be obtained from current vaginal administration systems (Table 1). However, there are also drawbacks, such as bioadhesive properties, distribution, release, and retention time. Over the past centuries, the focus has been given to gel-like formulations with improved bioadhesive properties by the use of carbopol or polycarbophil as polymeric material. Even though limitations have been overcome, further development is required and, hence, ease of use, residence time, uniform distribution of pharmaceutical agents, and optimal pH maintenance for vaginal epithelium, should be considered [23]. Vaginal drug delivery route is of great interest as the surface area for the bioadhesion of systems is extended. Therefore, retention time can be enhanced to up to 3 days and the release of pharmaceutical ingredients can be controlled. This results in possibility to lower dosing, reducing side effects of the compound. In addition, transmucosal polymers are capable of attaching to mucosal surface covering epithelial tissue [24–26].

The characterization of VDDS is essential to ensure their safety, efficacy, and quality, guided by pharmacopeia monographs and FDA guidelines [27]. Critical parameters include physicochemical properties, such as appearance, pH, and viscosity, ensuring compatibility with vaginal conditions. Drug content and uniformity are assessed to ensure consistent dosage and distribution of active ingredients. *In vitro* release and permeation studies evaluate the drug release rate and penetration into the vaginal mucosa, respectively. Stability studies, including thermal and mechanical stability, determine the shelf-life and optimal storage conditions. Mucoadhesion properties, including adhesion strength and retention time, are crucial for effective drug delivery. Safety evaluations encompass irritation, sensitivity testing, and microbiological testing to confirm the absence of harmful microorganisms. Biocompatibility and biodegradability are assessed to ensure materials do not elicit adverse responses and degrade safely within the body or environment [28]. Innovative VDDS developments, reflected in numerous patents, focus on sustained-release systems, mucoadhesive technologies, biodegradable polymers, and nanotechnology to enhance drug solubility, stability, and targeted delivery, improving therapeutic outcomes and patient compliance [29].

Although both systemic and local effects can be achieved via vaginal drug administration, the fact that mucosal membrane and vaginal secretion are not constant has to be taken into account, as well as the stage of menstrual cycle. This last factor is important due to the constant change in estrogen concentration, which affects the thickness of the mucosal surface: the higher the estrogen concentration, the thinner the mucus and, hence, the higher the permeability of the compound. Thus, it is of great importance to note that absorption takes place through mucosal membrane when administering pharmaceutical agents through the vaginal route. Among other advantages, avoidance of gastrointestinal and hepatic first-pass effects are two important ones. Moreover, high permeability of mucus results in a benefit when administering many molecules [6, 23].

More in detail, drug absorption takes place in the lumen and penetrates the membrane in three possible ways: transcellularly, paracellularly, and vesicular or receptor-mediated. It is of great importance to study drug penetration or permeation properties that can be tested via *in vitro* and *ex vivo* studies. Hence,

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Table 1. Vaginal dosage form (VDF) classification, advantages, and administration form, as well as examples of studies carried out for each vaginal dosage form.

VDF	*Administration form*	*Advantages*	*Example*	*Ref.*
Gels, creams and foams	Semi-solid	Versatility Patient compliance Reduce first-pass effect Local effect Minimal systemic effect	Antimicrobials can be encapsulated for treatment of e.g. HIV, herpes simplex virus, *Chlamydia trachomatis* and *Neisseria gonorrhea*. Antibacterial, birth induction and cervical ripening agents can also be administered. Generally based on mucoadhesive polymers (e.g. polyacrylic acid, HPMC, xanthan gum or alginates.)	[17]
Hydrogels	Semi-solid	Ease of use Bioadhesive polymers Prolonged residence time	To moisture and lubricate the vaginal cavity. Hydrogels can present other features such as pH regulation, contraception, labor inducers or antimycotic activity.	[18]
Intrauterine devices (IUD)	Solid	T-shaped carriers No time consuming	Contraceptive effect. A professional is needed to administer and remove these systems.	[19]
Rings	Solid	nonstop delivery of microbicidal complexes Faster release	Designed in the late 60s to retain active compounds in the vaginal cavity in order to treat infections, iron anemia, bone thinning and to control irregular or difficult periods.	[20]
Sponges	Solid	Ease of handling	Adhesion to the mucosal area and rehydration with the vaginal fluid gives viscosity to the system.	[21]
Tablets and suppositories	Solid	Exact dosing Ease of use Drug stability Easy storage Ease of manufacture Easy to administer	**Tablets:** either fast-disintegrating (spread and form a dispersion or gel by rapid swelling when in contact with the vaginal mucosa) or controlled-release systems (slow liberation of the pharmaceutical agent by attaching to the mucosa). **Suppositories:** capable of melting or dissolving by the use of lipophilic and hydrophilic components, respectively. The absorption can be increased by adding diffusion enhancers (e.g. bile salts and surfactants).	[22]

among other *in vitro* studies that aim to determine this property, transwell permeation study across a Caco-2 cell monolayer is well-established [30, 31]. The most commonly used *ex vivo* assays are the diffusion chambers, which can be either Ussing chamber or Franz cell. On one hand, Ussing chambers are systems that allow the use of rat or porcine intestinal tissue. Thus, the ability to mimic an *in vivo* environment, allowing the study of regional differences in intestinal absorption and the ability to examine differences in intestinal absorption between different species are some of the advantages that the Ussing chamber presents [32]. On the other hand, Franz cells have been commonly used to examine dermal drug permeability, although it can also be taken as a model to study the permeability of pharmaceutical agent across an intestinal tissue. The main advantages of this technique when comparing it to the Ussing chamber are higher permeability values for the markers and the use of a magnetic stirrer on the acceptor side that enables a better mixture [31, 33].

Ex vivo methodologies to study mucoadhesive and drug release properties of vaginal tablets can be divided into conventional methods and novel methods. As conventional methods, paddle or basket apparatus, also known as detachment study, can be found, which is based on the time that a sample requires to disintegrate totally or to detach from the mucosal area. In novel methodologies, flow-through test, also known as the inclined plane method, is widely used to determine the retention time of a sample to mucosal substrate. By using this method, the mucoadhesiveness of polymeric solutions, liquid or gel formulations can be tested. Moreover, this method has been employed to test mucoadhesive properties of systems presenting in situ gelling properties. The disadvantage of this method is that no solid or thick formulations can be studied [31]. Another commonly used study to determine the interaction between mucus and polymer is the rheometry. With this assay, mucus–polymer interaction can be studied due to the change in the flow behavior of the produced mixture. For this reason, on one hand, to study liquid systems, shear-steady measurements of viscosity are performed. On the other hand, oscillatory shear measurements of the mechanical viscoelastic moduli are used to study gel-like systems [34]. It is capable of determining viscoelastic properties under a thermostatically controlled environment. In addition, dynamic viscosity, elastic, and plastic modulus can be determined [31]. However, these methodologies present two main limitations, which are test volume and pH not being similar to the conditions needed for vaginal release. Thus, Kast *et al*. carried out a bettered simulation for *in vitro* release of clotrimazole from thioglycolated chitosan-based vaginal tablets. Furthermore, Woolfson *et al*. used a mixture of isopropanol and water as a release medium, which resulted in superior results for releasing dapivirine from tablets [35, 36].

Moreover, *in vivo* studies can also be performed to determine drug concentration in plasma or the amount of absorbed active ingredient. However, a difficulty appears when correlating *in vitro* and *in vivo* assays for novel non-oral drug delivery systems [37].

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Vaginal drug delivery systems

State of the art

While vaginal drug delivery presents notable advantages, continuous innovation is essential to overcome challenges, such as bioadhesion, drug retention, and controlled release. To address these limitations, various drug delivery systems have been developed, leveraging novel materials and advanced technologies to enhance efficacy and patient compliance. This section explores the latest advancements in vaginal drug delivery systems, focusing on both conventional and emerging approaches. The increasing interest in vaginal rings with controlled release of active ingredients over a prolonged time is requiring a standardization of the testing procedures [38–40]. Bassi *et al*. developed a dynamic vaginal system based on the evaluation of *in vitro* drug release from a bioadhesive vaginal film using as a testing method the inclined plane apparatus. The assay is based on the mucoadhesive properties as a function of the retention of the polymer in contact with the mucosa. Results exhibit efficient diffusion and swelling behavior, which result in greater drug release [41].

Although sponges are solid systems with advantages such as the ease of handling, certain criteria need to be accomplished, such as the adhesion to the mucosal area and the rehydration with vaginal fluid, which gives viscosity to the system. Hydroxyethylcellulose (HEC)-sponges were developed through the lyophilization of hydrogels made from cellulose derivatives and characterized in terms of mucoadhesion, rehydration ability, and stability [21, 42]. The importance of a quick rehydration of sponges is that this ability has a great influence on the mucoadhesive properties of the polymer and the slow elimination of the system. Furst *et al*. studied the impact of the pore size on the rehydration rate. Results exhibited that the rehydration speed of HEC sponges is not affected by the freezing temperature. Hence, sponges freeze-dried at 15°C did not rehydrate faster than sponges lyophilized at 35°C. However, the HEC concentration did have an impact on the rehydration time: the lower the concentration, the faster the rehydration. When studying how the pore size affected the rehydration process, it was seen that it does not have an impact [21].

Specific values for an optimal polymeric viscosity have not been determined due to the constant physiological changes in the vagina. However, viscosity is one of the most important parameters because of the role it plays in the retention time of rehydrated sponges in the vaginal cavity. Moreover, efficient vaginal distribution can be reached with suitable viscosity of the sponge [18]. Further experiments carried out by Furst *et al*. were aimed to measure the viscosity of sponges before lyophilization and after rehydration using cervicovaginal mucus (CVM) and comparing the three hydrogels tested (A, B, and C), which differed in the polymer concentration, from low to high, to two commercially available products: a vaginal cream, Gynodaktarin, and a lubricant, Lubrilan. Results (Fig. 1a) show a lower viscosity for hydrogel A, whereas hydrogels B and C presented viscosities in the range of the commercial products, concluding that the higher HEC concentrations, the higher the viscosity [21].

The last property of the hydrogels that was tested by Furst and the research group was the mucoadhesion. This parameter gives a prolonged retention in the vaginal mucosa. Thus, the mucoadhesive strength of different hydrogels was studied (Fig. 1b) comparing the results to the HEC 250M concentration and results exhibited that, the higher the polymer concentration, the higher the mucoadhesive strength. Hydrogels and sponges were examined using different measurement methods. Sponges appeared to be more adhesive than their corresponding hydrogels. The same commercial products as in the viscosity tests were used as reference values. The results showed that sponges have higher energy to adhere to a surface as opposed to the comparable hydrogels and reference products (Fig. 2c). Thus, the HEC 250M sponges fulfill the criteria of mucoadhesion and are more mucoadhesive than hydrogels [21].

Novelty in the field of vaginal hydrogels is the thermosensitive progesterone hydrogels in combination with mucoadhesive agents. Progesterone (P4) is a steroidal hormone present in the female reproductive system that has the main function to maintain normal physiology, proliferate normal breast tissue, regulate the sexual responsive signals in the brain, and protect against bone loss [44]. However, in the pharmaceutical field, P4 is used aiming to prevent preterm birth, luteal phase support, and hormone replacement therapy (HRT) [45, 46]. Almomen *et al*. examined the safety and effectiveness of hydrogels containing glycol chitin (GC) as a carrier or P4 (Fig. 2). *In vitro* and *in vivo* studies exhibited that GC is capable of managing vaginal properties, such as the acidic pH and the amount of mucin, better in comparison to P4. Results showed that increasing GC concentrations also increased P4 solubility. In addition, GC-P4 was able to form a stable hydrogel at body temperature within seconds and maintain this condition for hours. Furthermore, toxicity studies established that GC-P4 is safe to be used on murine vaginal epithelia. The addition of this MP indicated promising advantages for vaginal drug administration compared to the already existing P4 formulations [43].

Nanocarriers are systems capable of forming chemical and physical bonds with the mucus in the vagina and present properties that can be modified by increasing or decreasing their size or the chemistry of the surface. In general, mucoadhesion is one of the most important factors of vaginal drug delivery because of the natural cleansing system of the vagina. Through modifications with different mucoadhesive polymers (MPs), nanosystems acquire advantageous properties such as vaginal retention hence prolonged drug release [47–50]. Polymeric nanocarriers can be divided into nanospheres and nanocapsules. Nanospheres are matrix-like carriers, whereas nanocapsules have a liquid core that is surrounded by a polymer coating. Another type of nanocarrier represents polymersomes, amphiphilic, and, therefore, able to encapsulate hydrophilic and hydrophobic molecules [51]. In addition to polymer-based nanocarriers, there are other forms of administrations such as liposomes, solid-lipid nanoparticles, or nanoemulsions existing. However, the main goal of all of these carriers is to administer pharmacologically active molecules, such as low molecular-weight drugs, proteins, or siRNA [33]. Woodrow *et al*. showed polymeric nanoparticles as a possible method to deliver siRNA. Therefore poly(lactic-co-glycolic acid)-based nanoparticles in the size of 100-300 nm were developed and loaded with siRNA. After administration into mice vagina, results showed good distribution and penetration through mucosa. The safety of these nanosystems also was proved by toxicity studies of the research group [52].

Apart from these nanoparticulated systems, the novelty in the field is based on the 3D printing technology, which has

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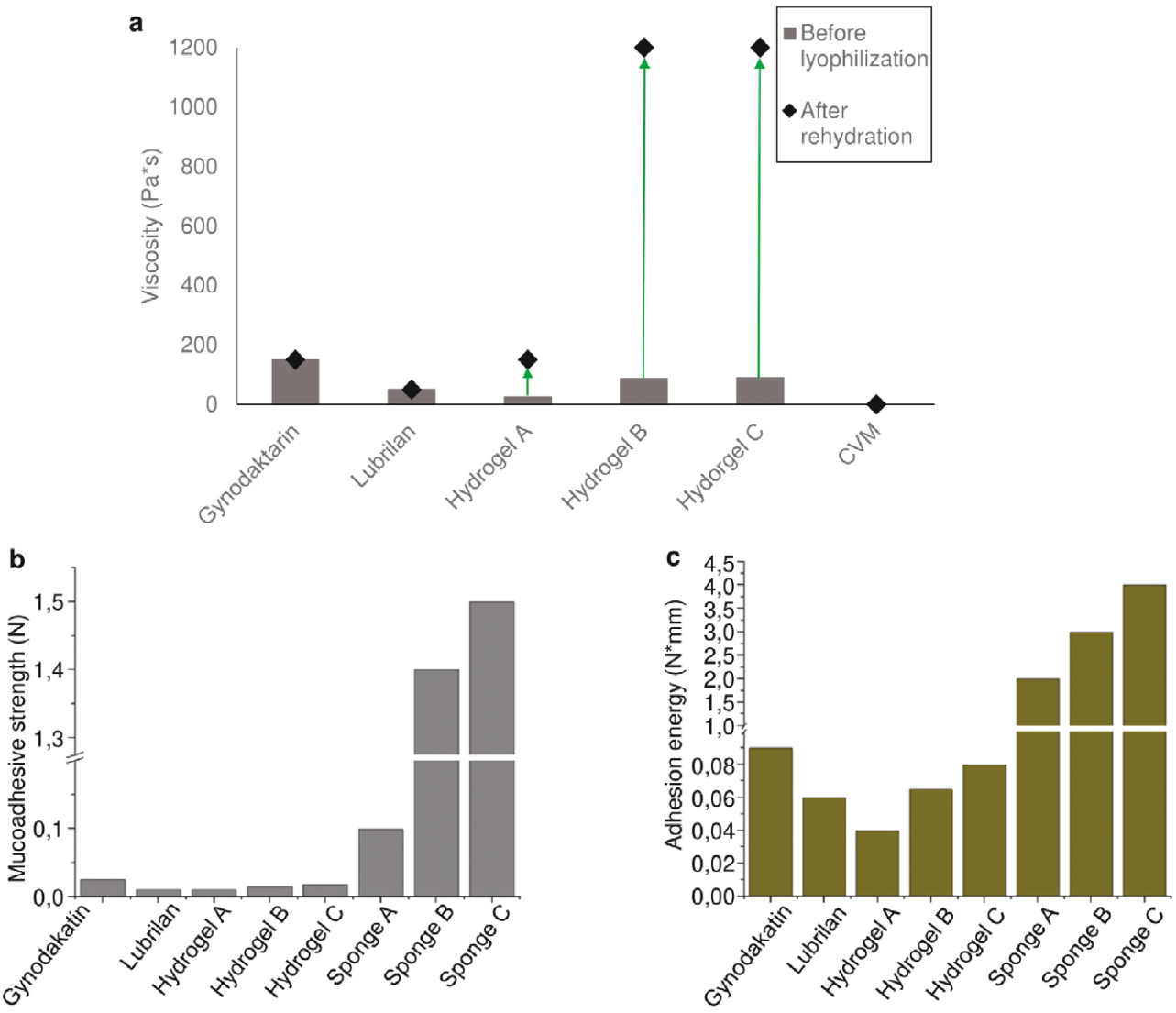

Figure 1. (**a**) Viscosity (Pa*s) of the two commercially available pharmaceutical hydrogels, Gynodaktarin and Lubrilan, CVM and the three HEC-hydrogels tested by Furst *et al.* before lyophilization and after rehydration, (**b**) mucoadhesive strength of hydrogels in comparison to sponges and (**c**) adhesion energy (N*mm) [21].

gained notorious interest over the past years. Since the first patent of the vaginal ring, an incredible progress in the area has been made. However, design and development methodologies can vary in a wide range. Among others, 3D printing can be found, which is based, for vaginal ring manufacturing, in fused deposition modeling (FDM) technology. Arany *et al*. aimed to develop a vaginal ring for clotrimazone release to treat vulvovaginal candidiasis using 3D printing. Results exhibited successfully printed thermoplastic polyurethane (TPU) vaginal rings, which were then filled with drug and gellifying agent. Further thermogravimetric and heat flow analysis showed the polymeric stability of the TPU during the printing process. Moreover, as the drug and gellifying agents were not mixed with the TPU before printing, but added afterwards, the method results to be adequate for all kinds of APIs without possible heat damage or API loss. In addition to this, ring resulted to be biocompatible and not toxic [53].

Another interesting novel technology is based on electrospinning. The electrospinning method is very commonly used to produce polymeric nanofibers encapsulating pharmaceutical agents. Over the past years, the electrospinning methodology has gained interest in the field, which is why different research groups are studying it. Tugcu-Demiröz *et al*. developed metronidazole (MET)-loaded nanofibers for treating bacterial vaginosis. Results exhibited that the polymers used for the study were all suitable for the electrospinning process and the drug release profiles were similar for all concentrations of polymer. In summary, the vaginal use of MET-loaded nanofibers has appeared to be of great interest as a potential VDDS [54]. Moreover, Zupancic *et al*. developed a biodegradable and biocompatible chitosan/polyethylene oxide nanofiber by using the electrospinning methodology to encapsulate MET. These were also positive in the studies for local vaginal infections [55].

Over the past decade, clinical trials (Table 2) for cervical cancer and HIV treatment have been carried out. As it can be observed, most pharmaceutical agents are still under study phase 3 due to the novelty of these therapies.

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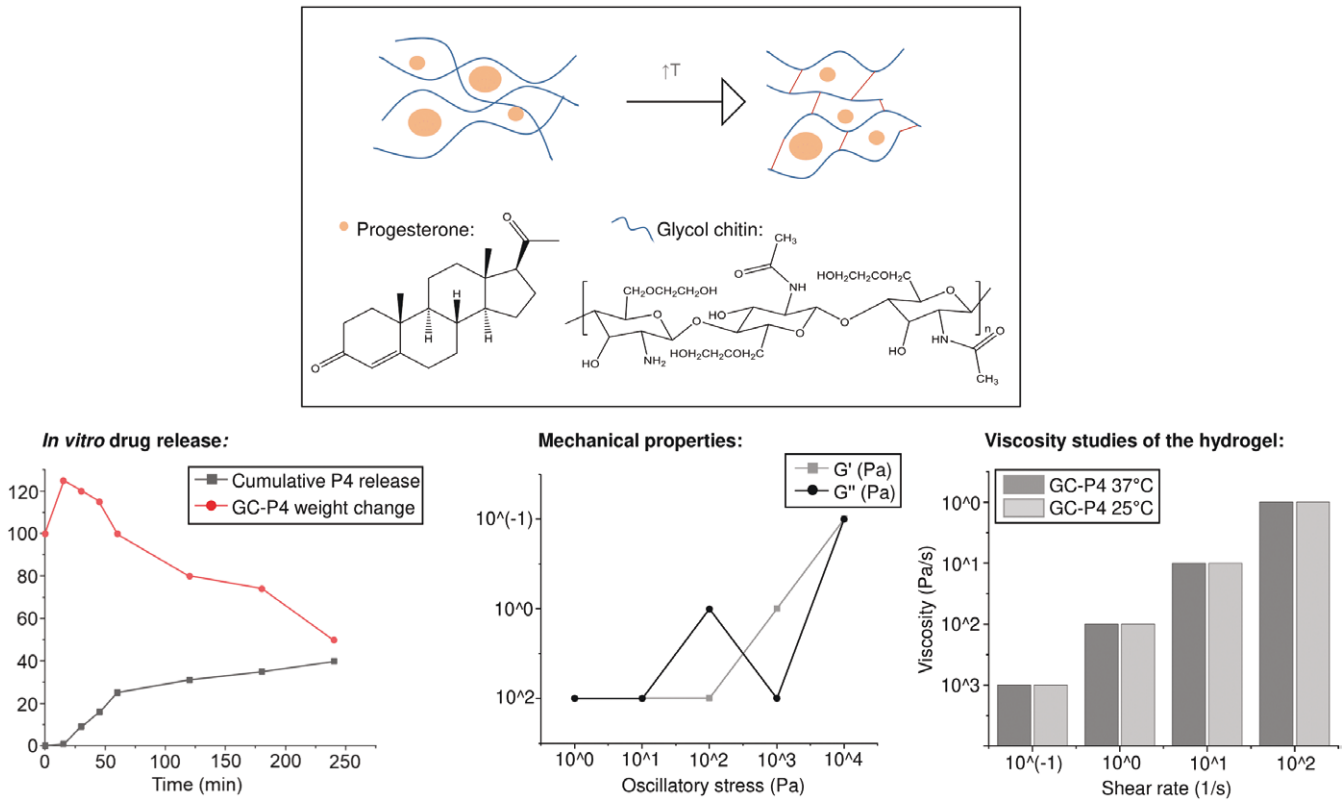

Figure 2. Research performed by Almomen *et al.* aiming to study a newly developed glycol-chitin (GC)-progesterone (P4) entrapping hydrogel for vaginal drug delivery and the results obtained for (**a**) *in vitro* drug release studies, (**b**) mechanical properties studies and (**c**) viscosity of the hydrogel studies [43].

Application of vaginal drug delivery sysems

The diverse range of vaginal drug delivery systems has enabled significant advancements in treating various conditions, from contraception to infection control and hormone therapy. One critical area of application is the management and prevention of sexually transmitted diseases (STDs), where controlled drug release and localized action offer a promising alternative to traditional systemic therapies. The following section delves into the application of vaginal drug delivery systems in the treatment and prevention of STDs, highlighting their therapeutic potential and clinical relevance.

Sexually transmitted diseases

STDs comprise a spectrum of infections transmitted via sexual contact, including chlamydia, gonorrhea, syphilis, human papillomavirus (HPV), herpes simplex virus (HSV), HIV/AIDS, trichomoniasis, and hepatitis B and C. The FDA has approved a variety of antiretroviral agents for HIV/AIDS therapy, categorized into Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Strand Transfer Inhibitors (INSTIs), and Entry Inhibitors. Representative combination antiretroviral therapies include Atripla (efavirenz, emtricitabine, and tenofovir disoproxil fumarate), Complera (rilpivirine, emtricitabine, and tenofovir disoproxil fumarate), Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), Triumeq (dolutegravir, abacavir, and lamivudine), and Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide). Additionally, examples of vaginal drug delivery systems include NuvaRing (etonogestrel and ethinyl estradiol), Annovera (segesterone acetate and ethinyl estradiol), and the dapivirine vaginal ring designed for HIV prophylaxis. These systems enable localized therapeutic action with controlled, sustained release of active agents, thereby reducing systemic side effects [56].

Cervical cancer treatment

The second most common gynecological cancer among women is cervical cancer, and it resists chemotherapy. The main cause of this type of cancer is the human papillomavirus (HPV), which is a small double-stranded DNA virus. HPV is among the most common sexually transmitted infections, and they are a significant cause of cervical cancer and other anogenital cancers. The development of vaginal drug delivery systems containing antivirals represents a promising approach for the treatment and prevention of HPV infections. These systems offer targeted delivery directly to the site of infection, enhancing drug efficacy and minimizing systemic side effects. Vaginal delivery systems such as gels, creams, foams, and intravaginal rings have been explored for their potential to deliver antiviral agents effectively. These formulations can provide sustained release of the antiviral drugs, maintaining therapeutic concentrations over extended periods and reducing the frequency of application. The use of mucoadhesive polymers in these systems can enhance the retention time of the drug at the mucosal surface, further improving the treatment's effectiveness. Including antiviral-containing vaginal systems in this compilation can highlight the advances in HPV treatment strategies and their potential impact on public health. Such systems not only provide an effective means of

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Table 2. Clinical trials for vaginal cancer and HIV treatment performed over the past decade and taken from ClinicalTrials.gov

Condition/Disease	*Sponsor and ClinicalTrials.gov Identifier*	*Official Title*	*Drug*	*Clinical Phase*
Cancer of the cervix	M.D. Anderson Cancer Center NCT01536392	Oral ondansetron versus transdermal granisetron (Sancuso) for women with cervical, endometrial or vaginal cancer receiving pelvic chemoradiation	Granisetron Ondansetron	Phase III
Cervical/Endometrial/ Ovarian/Vaginal Cancer Carcinoma of the Vulva	Dana-Farber Cancer Institute NCT00545792	A pilot study evaluating the safety of avastin and pelvic radiation in women with pelvic-confined recurrence of gynecological cancers	Avastin	Phase II
Cervical/Endometrial/ Ovarian/Vaginal/ Fallopian tube Cancer	Masonic Cancer Center, University of Minnesota NCT00381888	Women's cancer center protocol #45: prolonged venous Thromboembolism prophylaxis with fondaparinux in gynecologic oncology patients: an open label phase II trial	Fondaparinux sodium	Phase II
Cervical/Vulvar/Vaginal/ Genital Cancer	Merck Sharp & Dohme Corp. NCT01047345	A phase III, randomized, international, placebo-controlled, double-blind clinical trial to study the tolerability and immunogenicity of V503, a multivalent human papillomavirus (HPV) L1 virus-like particle (VLP) vaccine, given to females 12-26 years of age who have previously received GARDASIL™	V503 (Gardasil)	Phase III
HIV Contraception	CONRAD NCT02602366	The quatro study: acceptability study of (placebo) vaginal delivery forms for preventing HIV and unintended pregnancy among young women in Zimbabwe and South Africa	Placebo	Not applicable
HIV	National Institute of Allergy and Infectious Diseases (NIAID) NCT00540605	Phase I study of the maternal single-dose pharmacokinetics and placental transfer of tenofovir 1% vaginal gel among healthy term gravidas	Tenofovir	Phase I
HIV	International Partnership for Microbicides, Inc. NCT01144676	A double-blind, randomized, placebo-controlled pharmacokinetic and safety trial in healthy HIV-negative women to assess the delivery of Dapivirine from a matrix vaginal ring and to evaluate the safety of a matrix vaginal ring containing 25 MG of Dapivirine	Dapivirine	Phase I
Vaginal cervical cancer	National Cancer Institute (NCI) NCT00941070	A phase 2 study of Triapine® (NSC #663249) and Cisplatin in combination with pelvic radiation for treatment of stage IB2-IVa cervical cancer or stage II-IV vaginal cancer	Triapine Cisplatin	Phase II

delivering antiviral drugs but also empower women with self-administered, noninvasive treatment options. This approach aligns with the broader goals of improving women's health outcomes and reducing the burden of HPV-related diseases through innovative drug delivery technologies [57].

There are several emerging methods for assessing the intestinal and related mucosal areas, but these approaches require advanced knowledge in mucosal immunology and reproductive biology. Contemporary technologies, including single-cell RNA sequencing, mass cytometry, deep sequencing of bacterial 16S rRNA, and the internal transcribed spacer regions of fungal rRNA genes, along with metagenomics and metabolomics, are becoming increasingly significant in the fields of immunology and reproductive health. These techniques offer new possibilities for understanding these complex systems. The human vagina hosts a diverse array of microorganisms, collectively known as the vaginal microbiota. Research is increasingly revealing the intricate interactions between the host and this microbiota. Probiotics, which can influence the composition of the gut microbiota and restore a healthy bacterial balance, have potential health benefits. However, there is still limited research in this area, and scientific understanding is in its early stages. Further studies are needed to clarify whether changes in intestinal microbiota contribute to conditions like eczema or if these changes are a result of the condition itself. A deeper understanding of the interactions between vaginal microbiota and the host is essential. Developing novel strategies to monitor and manage vaginal microbiota could provide new avenues for disease treatment. Exploring these approaches might be more cost-effective compared to creating new anti-inflammatory drugs. There is an opportunity to advance probiotic treatments based on the interactions between specific microbiota and HPV infection, offering potential benefits for women's health [58, 59].

The actual treatment of cervical cancer is based on radiotherapy or surgery followed by chemotherapy. In the last

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years, many drug delivery systems (Table 3) have increased its interest in the treatment of cervical cancer due to their selectivity and the capacity to deliver active compounds to cancer tissues without affecting other ones [66, 67].

One drug that has shown relatively high antitumoral efficacy with low systemic toxicity for cervical cancer treatment is paclitaxel (PTX). Since more than 30 years, PTX was incorporated in solid lipid nanoparticulate (SLN) systems, which are composed of physiological and biocompatible lipids, ranging from 10 to 100 nm in size and with the capacity to be loaded with not only lipophilic but also hydrophilic pharmaceutical compounds. Among the advantages of SLNs, one is that these systems allow the sustained and controlled release of the drugs, as well as the biodegradable properties these present [64]. Moreover, mechanisms allowing the cellular uptake of siRNA have been explored recently for many different areas including cancer treatment [68]. A newly developed system based on the magnetic properties of iron oxide NPs exhibited notorious results for cancer treatment. It has been demonstrated that iron oxide generates reactive oxygen species (ROS), which have a potential activity against cancer cells. Iron oxide NPs in combination with an alternating magnetic field can lead to the generation of ROS and, therefore, cancer cell death [69].

Büyükköroğlu *et al.* developed vaginal suppositories for local treatment and therapy of cervical cancer. The research group designed a pharmaceutical system containing the chemotherapeutic drug, being PTX in this case, and genetic material (siRNA) capable of inhibiting the BCL-2 oncogene. These two agents and a combination of them were incorporated into solid lipid nanoparticles (SLNs), which were then dispersed in the vaginal suppositories previously prepared with PEG6000. In vitro studies exhibit that SLN formulations can release both siRNA and paclitaxel and a local effect is achieved. Moreover, the addition of paclitaxel lowers the toxicity of the systems and another advantage is the ease and self-administration that is possible by the suppositories [65].

To determine the release rate of the drugs in SLNs from suppositories, a horizontal diffusion chamber system (HDCS) was used, and to detect the presence of SLNs and determine the quantity of PTX and siRNA, high-pressure liquid chromatography (HPLC) and nano-drop were the two methods carried out. An increased amount of PTX and siRNA indicates an increase in the release of SLNs from the suppositories. According to the analytical results, SLNptx and siSLNptx were completely diffused into the receptor chamber from the suppository. The rapid release obtained in comparison to other SLNs may be due to the small particle size of siSLN and the consequent easy penetration through membrane pores. The in vitro experiments performed in this study demonstrated that co-release of siRNA and paclitaxel is possible with SLN formulations. Vaginal administration of the suppositories bearing the SLN system allowed local release of the chemotherapeutic PTX at the target site. Thus, the drug dose entering the systemic circulation was decreased and the toxic effects were reduced. In addition, the suppositories provide the possibility of self-administration without the need for professional assistance [65].

Upadhyay *et al.* evaluated the in vivo efficacy of doxorubicin (DOX)-loaded poly(γ-benzyl l-glutamate)-block-hyaluronan (PBLG23-b-HYA10)-based polymersomes (PolyDOX). PolyDOX was used in the treatment of cancer and proved to delay tumor growth and lengthen lifespan compared to free DOX. Results (Fig. 3) showed PolyDOX to be safe, side effects decreased and the therapeutic index improved [62].

Another type of system for cervical cancer treatment is by the use of liquid crystals (LC) that are able to solubilize oil and water-soluble compounds due to their microstructure and physiochemical properties. Hence, LC are good candidates as carriers for hydrophilic and hydrophobic compounds [70]. Among the advantages that liquid crystals present, a sustained drug release, improved drug permeation, and accelerated drug absorption are three of notorious interest in the pharmaceutical field [71, 72].

David *et al.* developed and evaluated curcumin LC systems for cervical cancer treatment. Some physicochemical properties of curcumin, such as low aqueous solubility, made it a need to evaluate novel formulations for its administration. The LC system was designed to contain a surfactant, glycerol,

Table 3. Summary of some cervical cancer treatments under study, results of each study and the drug and vaginal dosage form used.

Vaginal Dosage Form	*Drug*	*Results of the study*	*Ref.*
Liquid crystals	Curcumin	Higher encapsulation efficiency.	[60]
Patch	5-Fluorouracil	Penetration of the drug into cervical tissue is achieved to up to 5.5 mm of depth. The higher the concentration of drug in the patch, the higher the concentration of drug in the cervical tissue.	[61]
Polymersomes	Doxorubicin	Tumour growth was delayed, lifespan was improved, system was safe, side effects decreased and therapeutic index increased.	[62]
Polymeric Nanocapsules	Imiquimoid	Increased drug performance against tumor cells due to nanoencapsulation. Enhanced mucoadhesion, permeation and drug retention.	[63]
Suppository	Bleomycin, carhazilquinone and 5-fluorouracil	Treatment previous to surgery. Eradication of tumor lesions of 51.5% and 21.43% of the patients at stage 0 and I, respectively.	[61]
SLN	Paclitaxel	Sustained and controlled release of the drug.	[64]
SLN	Combination of paclitaxed with siRNA	Controlled release of paclitaxel and siRNA and local effect is achieved. Less toxic effects.	[65]
Sponge	Retinoid (TRA)	Higher dosing exhibited milder cervical inflammation. No systemic effects were shown.	[61]

SLN: solid lipid nanoparticle.

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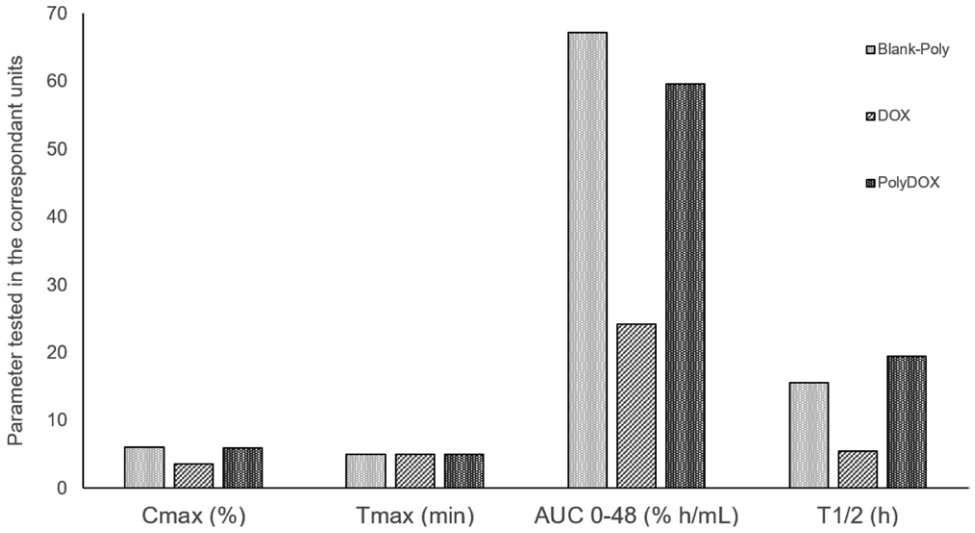

Figure 3. Comparison of pharmacokinetic parameters tested and the units of each of them for three different samples: the blank polymer (Blank-poly); the doxorubicin as drug (DOX) and the DOX-loaded poly(γ-benzyl l-glutamate)-block-hyaluronan (PBLG23-b-HYA10)-based polymersomes (PolyDOX) [62].

and water, as well as curcumin. A ratio of curcumin:Tween80 of 0.5:60 or 1:60 was found to be preferred because it presents a higher encapsulation efficiency. These two formulations were further analyzed using ATR-FTIR and the microstructure was characterized by environmental scanning electron microscopy (ESEM) [60].

Human Immunodeficiency virus

Nanotechnology has allowed the development for preventing HIV transmission focusing on microbicides carried by polymer-based nanocarriers. Schäfer *et al*. obtained results showing the influence of size and surface composition on the uptake rate by macrophages. Nanoparticles in this study were based on polymethylmethacrylat and albumin and the uptake rate of these zidovudine-loaded nanoparticles by macrophages increased up to 60% more in HIV-infected cells compared to non-infected macrophages [73].

Over the past decade, nanovaccinology has gained interest, especially when using gold nanoparticles as carriers for antigens since these can be easily shaped [74, 75]. Xu *et al*. compared recent research in adjuvants for HIV vaccines. They evaluated different surface-modified gold nanorods (AuNR) which were used as carriers in the treatment of HIV. Surface was modified with cationic molecules such as poly(diallydimethylammonium chloride) (PDDAC) and polyethyleneimine (PEI). Results exhibited the DNA delivery into nucleus was possible after the cells were treated 3 h with PDDAC-AuNR-DNA and PEI-AuNR-DNA complexes [76].

Although research has been focusing on the development of an effective and safe vaccination system against HIV, there is still room for improvement in this field. For instance, studies targeting vaginal mucosa are of notorious interest to gain protective mucosal immunity. Despite the fact that vaccination against HIV has been studied for more than two decades under clinical trials, there are limiting factors that result in drawbacks for the development of systems. Firstly, anatomical differences between species explain the great translating results obtained from *in vivo* studies. Furthermore, there are added complications existing, such as the changes in menstrual cyclicity as well as exogenous hormones modulation vaginal immunity. These are difficult to control in human trials unlike animal studies [77].

Several drug delivery systems aiming for HIV vaccination (Table 4) have been studied. The main challenge was to avoid the leaking of free-flowing liquid vaccines from the vaginal cavity. Thus, solid dosage formulations have gained interest in the field to overcome this problem. Using vaginal gels improve significantly the ability to encapsulate pharmaceutical agents such as antigens and adjuvants. Hence, these systems are commonly developed, improved, and under study in the vaginal administration route field [77]. Furthermore, the use of jet injectors is also a promising approach for the vaginal delivery route. These are based on the delivery of liquid vaccines through a nozzle orifice at elevated speed, leading to the effective penetration in the upper epithelial mucosal layers. The result can be seen as an enhanced antigen uptake. A vaginal vaccination model by the use of jet injectors resulted in an increase the secretion of vaginal IgA and IFN-γ in comparison to syringe-based vaccines [80].

Further studies carried out with polymeric nanoparticles resulted in notorious advantages for vaginal drug delivery. Studies based on the delivery of antiretroviral drugs and siRNA have been carried out over the past years for a potential treatment of HIV prophylaxis. *Ex vivo* permeation experiments through vaginal mucosa and *in vivo* studies using female swine concluded with enhanced penetration of the drug, an inhibitory peptide (E2), constituting an approach as an alternative to inhibit HIV infections [81].

Over the past decades, implant-based technologies have gained interest in the HIV field. A newly developed and under regulatory review vaginal ring that has exhibited a percentage of between 27 and 31 in reducing the possibilities to acquire the HIV. However, not enough information is known at the moment. Furthermore, there are vaginal formulations to deliver certain active ingredients under clinical trials to prevent HIV transmission. Among vaginal rings under phase 1 of the clinical trials, we can find tenofovir in combination

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with levonogestrel, as well as elvitegravir in combination with tenofovir alafenamide (TAF) [27].

In addition, core-matrix intravaginal rings using fused deposition modeling 3D printing are under study and development to reduce the risk of HIV infections as well as prevent unintended pregnancy. *In vitro* and *in vivo* evaluations indicated a continuous drug release up to 28 days with the developed polymeric microneedles containing a pharmaceutical agent, resulting in positive hypothesis for a multipurpose vaginal ring (Fig. 4) [82].

Novel pre-exposure prophylactic bioadhesive formulations containing TDF represent a promising strategy for preventing HIV acquisition in uninfected individuals. These formulations utilize bioadhesive polymers to enhance mucoadhesive strength, extend drug release, and increase residence time on the vaginal mucosa. The small size and high surface-to-volume ratio of bioadhesive particulate systems facilitate concentrated and effective delivery at the site of action, improving their efficacy in preventing HIV transmission during intercourse. While long-acting systemic formulations are a growing focus in HIV prevention, intravaginal dispersible tablets offer an innovative on-demand solution for both men and women [83]. Multipurpose delivery systems, such as vaginal rings designed for simultaneous HIV prevention and contraception, represent a promising advancement in the field of vaginal drug delivery. These systems offer the unique advantage of addressing multiple health concerns with a single, convenient device, thereby improving patient compliance and reducing the need for multiple interventions. Vaginal rings, for example, can deliver a controlled, sustained release of active ingredients like antiretroviral drugs for HIV prevention and hormonal agents for contraception, all while minimizing systemic side effects [84].

However, the feasibility and clinical implications of these multipurpose systems come with certain challenges. One

Table 4. Drug delivery solid systems under study for vaginal application to protect against HIV disease.

Dosage form	*System*	*Pharmaceutical agent*	*Results*	*Reference*
Gel	Thermosensitive polaxamer	RANTES-expressing plasmid (pRANTES)	Enhanced mucosal and systemic immune responses	[77]
Nanosystems	PEG nanoparticles	Inactivated HIV-1	Enhance retention time, penetration through mucus, cellular targeting and self-adjuvanting systems.	[77]
Nanosystems	PEG amino nanocomplexes	HIV-gag protein expressing adenoviral vector	Enhanced permeation through mucus, enhanced delivery of genetic material.	[77, 78]
Rheologically structured vehicle gel	HEC	HIV-1 CN54 gp140	Enhanced exposure of antigen to mucosa but modest antibody response.	[77]
Solid	Vaginal HPMC rings and disks	HIV-1 CN54gp140 protein	Enhanced residence time of the antigen in the mucosal area. Hence, enhanced mucosal antibody response to protein immunogens.	[77, 79]

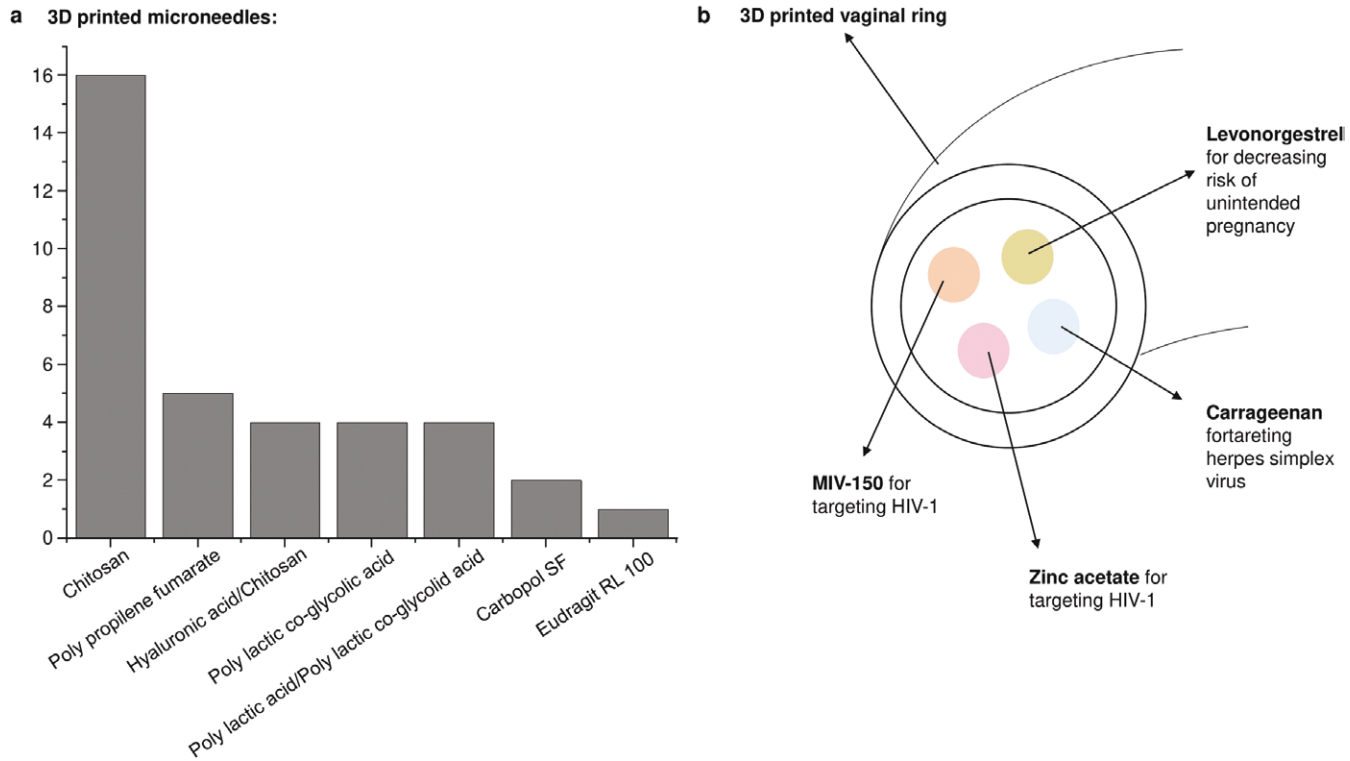

Figure 4. Design and development of novel 3D printed (a) different polymeric microneedles encapsulating a pharmaceutical agent and their release time and (b) vaginal rings and drugs that can be encapsulated in the core of the 3D printed polymeric system [82].

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Table 5. Classification of complicated genital infections and division in main causative reason, as well as treatment carried out to overcome each infection and examples for active pharmaceutical ingredients (API) used in therapies.

UTI	Reason	Treatment	Example of API
Vesicoureteralreflux	Congenital	**Medium/low degree:** Reflux resolves spontaneously. **High degree:** Anticholinergics and antibiotics.	Ciprofloxacin
Polycystic kidney	Congenital	Antibiotics	Ciprofloxacin
Pelviureteric junction obstruction	Congenital	Surgery—catheter	-
Urinary diversion	Functional	Surgery—bladder replacement	-
Intermittenself-catheterization	Functional	Surgery—removal	-
Urinary tract instrumentation	Functional	Antibiotics	Ciprofloxacin Cefotaxim
Diabetes	General condition	Antibiotics	Ciprofloxacin Cefotaxim
Renal transplant	General condition	Antibiotics	Ciprofloxacin Levofloxacin
Immunosuppression	General condition	Antibiotics	Amoxicillin Clavulan

primary challenge is ensuring the compatibility of the different active ingredients within the same delivery system. The drugs must not only maintain their stability and efficacy when combined but also be released in a manner that achieves therapeutic concentrations for each indication. Furthermore, there are concerns regarding patient acceptability and the potential for discomfort or irritation, as some individuals may experience localized reactions to long-term device use. In addition, designing these systems requires careful consideration of factors like drug interactions, dosing schedules, and the ease of use, as well as addressing concerns about the long-term safety of devices that remain in the body for extended periods [85, 86].

Clinical implications also extend to the need for rigorous testing in diverse patient populations to assess both safety and efficacy. While multipurpose vaginal delivery systems have the potential to simplify treatment regimens and improve adherence, their development must be approached with a comprehensive understanding of the specific medical, pharmacological, and patient-centered factors that will impact their success in real-world settings. Expanding the discussion on these systems could provide a clearer perspective on the potential benefits, risks, and clinical applications in addressing multiple health concerns simultaneously [85].

Furthermore, systems for pre-exposure prophylaxis (PrEP) and treatment as prevention (TasP) were evaluated by Brizzi *et al*. [87]. Early HIV treatment regimens required patients to take multiple tablets several times a day. The approval of the first fixed-dose combination tablet, lamivudine/zidovudine (3TC/AZT), in 1997 marked a significant advance, though it is now less common due to AZT's side effects. This development paved the way for further innovations, including the 2006 introduction of the first single-tablet regimen (STR) combining efavirenz/FTC/TDF, which reduced the pill burden to one daily pill. Since then, over ten additional STRs have been introduced, offering advantages such as reduced toxicities, fewer drug interactions, increased patient satisfaction, and cost savings. In 2021, the long-acting intramuscular combination of cabotegravir/rilpivirine (CAB/RPV-LA) was introduced, providing an alternative to daily pills with monthly or bi-monthly injections, improving adherence by addressing challenges like pill fatigue and drug interactions [88].

Fungal and bacterial infections

Although genital infections are notoriously common among population, women are more prone to suffer it. There are mainly two types of genital infections: uncomplicated and complicated. The first one develops in healthy women with no abnormalities in the urinary tract and no further dysfunctions. Infections corresponding to the second type (Table 5), however, present symptoms such as dysuria and pain, among others [89].

Among genital infections, bacterial vaginosis, *Trichomonas vaginalis* and vulvovaginal candidiasis are the most common. In Europe, the prevalence of bacterial vaginosis and vulvovaginal candidiasis are 5–15% and >60% in Caucasian women, respectively [90].

Antifungal and antibiotic treatment is not always effective for treating genital infections. Microbial resistance, side effects, and recurring infections are three limitations of the mentioned therapies. Therefore, the combination of probiotics is gaining interest. More in detail, bovine lactoferrin and lactoferrin-resistant probiotics in combination resulted in significant inhibition of bacteria in *in vitro* studies. Furthermore, clinical trials exhibited positive prevention of vaginal infections of different origins when associating probiotics and prebiotics [91].

Another clinical assay carried out by Mirzaeei *et al*. determined no complications for women treating vulvovaginal candidiasis with chlorhexidine vaginal gel. The clinical trial included Patients with vaginal discharge presenting at our University Gynecology Clinic. Data were analyzed using SPSS software. Quantitative data were analyzed using the student *t*-test, while ordinal data were analyzed using the Mann–Whitney *U* test. Qualitative data were analyzed using the Chi-square or Fischer's exact tests. For vulvovaginal candidiasis patients, the mean satisfaction score was 9.06 with chlorhexidine gel and 8.29 with clotrimazole cream. The Mann–Whitney test showed no significant difference in satisfaction scores (P = 0.027). In bacterial vaginosis patients, the mean satisfaction scores were 8.91 with chlorhexidine gel

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and 8.72 with metronidazole tablets ($P = .607$). In nonspecific vaginitis patients, the mean satisfaction scores were 8.83 with chlorhexidine gel and 9.17 with the combination of metronidazole and clotrimazole cream ($P = .401$). The combination therapy group had the highest mean visual analog scale (VAS) score. Chlorhexidine vaginal gel was found to be more effective than clotrimazole cream alone for vulvovaginal candidiasis. It also showed positive therapeutic effects as a single agent in nonspecific vaginitis, suggesting its benefits over the simultaneous administration of two agents [92].

Other diseases

Other diseases or conditions that require vaginal drug delivery systems can be chlamydia, gonorrhea, genital herpes, vaginal atrophy, menstrual disorders, or endometriosis, among others [93–95].

Chlamydia trachomatis (*C. trachomatis*) stands as the leading reason for microbial sexually transmitted diseases, posing significant reproductive tract complications for females. With concerns over approved oral antibiotics and the rise of antimicrobial resistance, alternative treatment avenues are imperative. This study introduced a novel approach, utilizing the natural polyphenol resveratrol (RES) within an innovative delivery system comprising liposomes embedded in chitosan hydrogel for localized C. trachomatis infection treatment. Through *in vitro* experiments using McCoy cells, both free RES and RES liposomes-in-hydrogel demonstrated concentration-dependent inhibition of *C. trachomatis* propagation. Notably, at lower concentrations, the anti-chlamydial efficacy of RES was notably augmented when incorporated into liposomes-in-hydrogel, with inhibition rates of 78% and 94% for RES liposomes-in-hydrogel at 1.5 and 3 μg/ml, respectively, compared to 43% and 72% for free RES. Additionally, RES liposomes-in-hydrogel exhibited potent anti-inflammatory activity *in vitro*, evidenced by concentration-dependent suppression of nitric oxide production in LPS-induced macrophages (RAW 264.7). The synergistic mixture of a natural compound with diverse pharmacological properties and an advanced delivery system offering enhanced activity and vaginal applicability holds promise for the localized treatment of *C. trachomatis* infection [96].

Gonorrhea, caused by the Gram-negative diplococcus Neisseria gonorrhoeae, stands as a prevalent sexually transmitted disease. While often asymptomatic in females, symptoms such as dysuria, vaginal discharge, abnormal uterine bleeding, dyspareunia, and lower abdominal, and rectal pain may manifest. Left untreated, complications, including pelvic inflammatory disease, chronic pain, and increased HIV transmission risk can arise. Standard treatment involves oral or intramuscular administration of antibiotics like cefixime or ceftriaxone. However, rising antimicrobial resistance poses challenges, leading to the exploration of alternative options such as dual antibiotic therapy. Despite these efforts, treatment failure remains common. Consequently, the development of new antibiotics, including macrolides, tetracycline derivatives, and broad-spectrum fluoroquinolones, is crucial in addressing Neisseria gonorrhoeae antimicrobial resistance [58].

Various therapeutic approaches are available to address infections caused by herpex simplex virus (HSV)-1 and HSV-2. These include synthetic antiviral medications, extracts from plants, compounds derived from plants, treatments based on algae, therapies using fungi, and advancements in nanotechnology. Several modern antiviral medications are available to treat HSV-1 and HSV-2 infections, primarily focusing on inhibiting viral replication. A major class of these drugs consists of acyclic nucleoside and nucleotide analogues, which work by interfering with viral DNA polymerase and preventing the extension of the viral genome. Acyclovir (ACV) is the most commonly used first-line treatment. It must be converted intracellularly into its active form, acyclovir triphosphate, by the viral enzyme thymidine kinase. This conversion enables ACV to act as a substrate for viral DNA polymerase, thereby inhibiting DNA synthesis and reducing viral replication. In addition to acyclovir, other antiviral agents such as valacyclovir, penciclovir, and famciclovir are frequently used [97]. Valacyclovir is a prodrug of acyclovir with improved oral bioavailability and better intestinal absorption. Penciclovir, developed to be phosphorylated more rapidly than acyclovir, has a longer half-life, allowing for less frequent dosing. Famciclovir, which converts into penciclovir in the body, also offers higher oral bioavailability and is used for treating both genital herpes and orolabial herpes. These drugs generally alleviate symptoms and reduce lesion duration more effectively than untreated conditions, with differences in their pharmacokinetic profiles influencing their specific applications. Valacyclovir and famciclovir, in particular, are approved for managing various clinical manifestations of HSV infections, including cold sores and recurrent genital herpes [98, 99].

The primary focus of research in vaginal drug delivery revolves around achieving localized action, addressing a spectrum of diseases and conditions such as bacterial, viral, and fungal infections, as well as vaginal atrophy and dryness. These conditions naturally occur within the vaginal environment. However, vaginal drug delivery systems also serve systemic purposes. Hormone delivery for menopause management and contraception stands as the most extensively studied areas. Additionally, vaginal formulations are under investigation as potential preventive agents against sexually transmitted diseases, including HIV infections. Challenges arise due to physiological features of the vagina, notably the high variability in vaginal conditions, such as fluid amount, composition, and pH. Moreover, these conditions exhibit intra-individual variability, potentially leading to diverse therapeutic responses within the same subject. Addressing these challenges is crucial for the advancement of effective vaginal drug delivery systems [28].

Hormone administration via the genital tract plays a crucial role in areas such as contraception and hormone replacement therapy. Nonetheless, the treatment used is dependent on the condition. For instance, the risk of venous thromboembolism (VTE) associated with hormone replacement therapy (HRT) varies depending on the route of estrogen administration. Research consistently indicates that oral HRT is linked to a higher VTE risk compared to transdermal HRT among postmenopausal women. Additionally, the type of progestogen used alongside estrogen has been identified as a factor influencing VTE risk. Although transdermal HRT appears to pose no increased VTE risk for healthy women without a history of thrombotic issues, evidence is sparse for those with a history of thrombosis or thrombophilia, and results from one population may not be applicable to another. The assessment of VTE risk with HRT should be personalized based on each

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woman's medical history. A history of VTE does not automatically rule out HRT use, but thorough counseling about the risks and exploration of alternative treatments is essential. If HRT is deemed appropriate, low-dose transdermal estrogen combined with oral micronized progesterone or a levonorgestrel intrauterine system (IUS), if necessary, is recommended. While estradiol dosage itself may not directly influence VTE risk, choosing the lowest effective dose is advisable. However, data on the safety of levonorgestrel IUS in women with thrombosis risk are limited, and further research is needed. In some high-risk cases, anticoagulation might be required, and this should be managed in consultation with a hematologist. Routine thrombophilia screening before starting HRT is not standard, but should be considered for women with a significant personal or family history of VTE. Having a heritable or acquired thrombophilia does not automatically contraindicate HRT, but transdermal options should be considered after a thorough evaluation of potential benefits and risks [100]. Another example of hormone replacement therapy was given by Petrone *et al*. in a review where the complex interactions between gender, hormonal factors, and the progression of autosomal dominant polycystic kidney disease (ADPKD), highlighting the current limitations were written. It explores how female sex hormones affect liver and renal manifestations, revealing gender-specific differences in disease progression. Women with ADPKD generally show slower renal disease progression compared to men, likely due to hormonal influences. The review examines how estrogen impacts the renin–angiotensin–aldosterone system, with implications for cardiovascular and renal health. The challenges of hormonal therapy in women with ADPKD are discussed, particularly concerning its effects on liver health and disease outcomes. The review emphasizes the need for individualized treatment strategies, including contraception options for premenopausal women, and evaluates the potential benefits and risks of hormone replacement therapy for those who are postmenopausal. The review concluded by stressing the importance of personalized treatment approaches and calls for further research to improve understanding of hormonal therapies in ADPKD. This research is vital for developing effective, tailored treatment options that address the specific needs and risks of each patient [101]. Several strategies and technologies can be employed to achieve personalized vaginal drug delivery. For instance, patient-specific devices such as vaginal rings can be designed to release drugs at varying rates based on the patient's needs, which can be determined through biomarkers or monitoring of therapeutic levels in bodily fluids. Advances in bioelectronics, such as sensors integrated into vaginal devices, allow for real-time monitoring of vaginal pH, temperature, and drug concentrations, enabling dynamic adjustments to the drug release profiles. Furthermore, the use of personalized formulations based on pharmacogenomics, where the drug's characteristics and release patterns are optimized based on genetic factors, can improve both efficacy and safety [102].

Technologies such as microarrays or microelectromechanical systems could also enable more precise control over drug release, providing personalized therapy based on individual requirements. Additionally, 3D printing technologies allow for the customization of vaginal drug delivery devices, ensuring that their size, shape, and drug-loaded content are tailored to fit the patient's unique anatomical and therapeutic needs [103].

Future perspective

The future of vaginal drug delivery systems is poised for significant advancements through the integration of personalized medicine and nanotechnology. Personalized drug formulations, tailored to individual hormonal profiles and specific health needs, are anticipated to revolutionize treatment efficacy and patient satisfaction. Advanced drug carriers such as nanoparticles, liposomes, and dendrimers are expected to enhance drug stability, control release, and improve absorption, while smart polymers and hydrogels that respond to physiological conditions like pH and temperature will offer more precise and effective treatment options. For instance, local irritation and sensitivity are indeed important challenges in vaginal drug delivery, and addressing them is crucial for ensuring patient comfort and the overall effectiveness of the treatment. To mitigate these side effects, formulation adjustments can be made by selecting biocompatible, nonirritating excipients, such as pH-buffered systems that match the vaginal environment, or incorporating moisturizing agents to reduce dryness and irritation. Additionally, the use of mucoadhesive polymers that gently adhere to the vaginal mucosa without causing friction or discomfort can help enhance both retention and tolerance.

From a delivery system perspective, modifications such as the development of slow-release systems (e.g. vaginal rings or films) can reduce the frequency of application, minimizing potential irritation from repeated exposure. Furthermore, incorporating advanced materials like thermosensitive hydrogels or biodegradable polymers can offer controlled drug release while ensuring that the system remains nontoxic and compatible with vaginal tissues. Such adjustments not only address the issue of irritation but also improve patient acceptability by enhancing comfort and reducing the likelihood of adverse reactions. By exploring these formulation and system modifications, the potential for vaginal drug delivery systems to achieve both efficacy and tolerability can be significantly improved.

Enhanced mucoadhesive systems and targeted therapies represent another promising avenue for the future. By improving the adhesion properties of drug formulations, these systems can prolong residence time and increase bioavailability. The development of biodegradable polymers will minimize side effects and eliminate the need for removal. Furthermore, targeted delivery systems will allow for localized treatment of conditions, such as vaginal infections, cancer, and sexual dysfunction, with minimal systemic exposure. The exploration of gene and protein delivery via the vaginal route could open new possibilities for treating genetic disorders, infections, and hormonal imbalances.

Improving user experience and integrating digital health technologies will also play a crucial role in the future of vaginal drug delivery systems. User-friendly applicators and discreet, portable options will enhance convenience and privacy for patients. The combination of drug delivery systems with smart devices and mobile apps will facilitate real-time monitoring of treatment progress, dose reminders, and feedback to healthcare providers. Telemedicine will further enable remote monitoring and timely adjustments to treatment plans. Efforts towards the harmonization of regulatory guidelines and the development of sustainable, eco-friendly formulations and packaging will ensure the safety, efficacy, and environmental sustainability of these advanced drug

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delivery systems, ultimately enhancing women's health and wellbeing.

Conclusions

Vaginal drug delivery systems offer significant advantages in achieving targeted therapy, particularly for conditions such as vaginal infections where high local concentrations of antimicrobial agents are required. By directly administering drugs to the vaginal mucosa, these systems can exert their effects locally, minimizing systemic exposure and side effects. This targeted approach is beneficial in effectively eradicating pathogens while preserving the body's natural microflora. Additionally, vaginal drug delivery systems enhance bioavailability and provide prolonged drug release kinetics compared to conventional administration routes. The vaginal mucosa's large surface area facilitates rapid and efficient drug absorption into the systemic circulation, and certain formulations, such as sustained-release inserts or rings, ensure sustained drug release over extended periods. This reduces dosing frequency and improves patient adherence to treatment regimens.

Beyond traditional therapeutics, vaginal drug delivery holds promise for innovative applications, including the delivery of vaccines, gene therapies, and other biologics. Research is ongoing to leverage the vaginal mucosa's immunomodulatory properties and its potential to induce both mucosal and systemic immune responses. Diseases affecting a significant percentage of women worldwide are increasingly being treated using vaginal drug delivery systems, available in both solid and semi-solid forms. This growing interest is driving continuous research and development aimed at improving efficacy and patient compliance. Innovative delivery systems can enhance patient compliance by focusing on user-friendly designs, such as discrete, convenient forms like vaginal rings, which can offer sustained release and require minimal patient intervention. Additionally, thermosensitive or bioadhesive formulations that ensure comfort and retention within the vaginal cavity may further increase the likelihood of consistent use.

To further enhance compliance, the development of personalized drug delivery systems could play a key role. For example, systems that allow for self-administration, such as easy-to-use applicators or discreet rings, may improve the overall experience for the patient, reducing the stigma often associated with vaginal treatments. Moreover, formulations that reduce the frequency of application, provide long-lasting effects, or minimize systemic side effects can help increase adherence to therapy. By integrating these features into the design of novel delivery systems, the goal of improving patient compliance can be better achieved. Thus, vaginal drug delivery systems represent a critical and dynamic area in the pharmaceutical field, with substantial implications for women's health.

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Author contributions

Eva Sanchez Armengol: Writing first draft and review; Florina Veider: visualization, editing; Gioconda Millotti: writing and reviewing; Gergely Kali: writing first draft; Andreas Bernkop-Schnürch: conceptualization, editing; Flavia Laffleur: conceptualization, writing, editing, and reviewing.

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Conflict of interest

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