Mucoadhesive Drug Delivery for Sexually Transmitted Infection Prophylaxis: Multipurpose Prevention Technologies and Combination Formulations

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Graphical Abstract

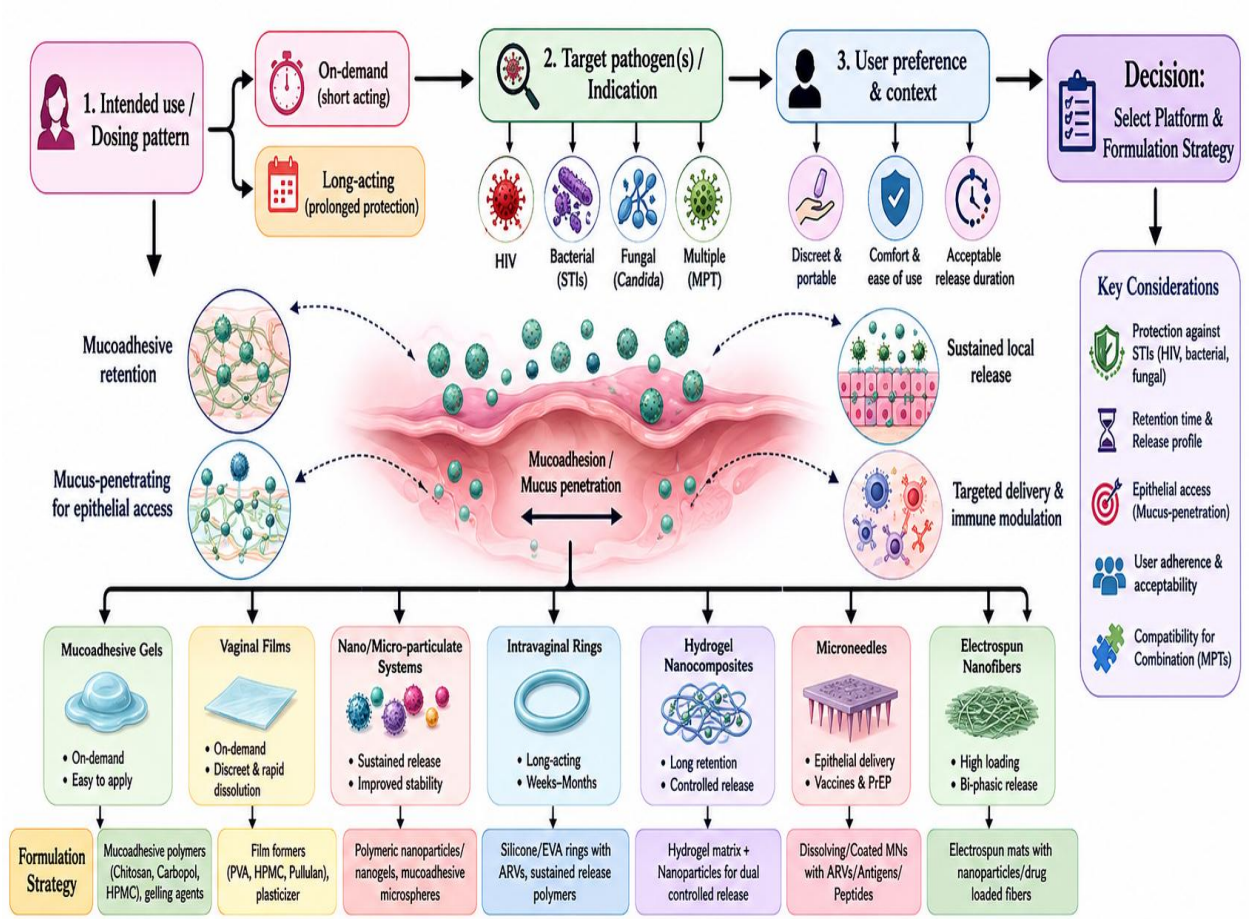

Figure 1: Graphical abstract for mucoadhesive drug delivery for sexually transmitted infection prophylaxis: multipurpose prevention technologies and combination formulations

Abstract

Sexually transmitted infections (STIs) remain a critical global public health challenge, with over one million new infections reported daily. Conventional preventive strategies often fail due to poor adherence, limited spectrum of protection and emerging antimicrobial resistance. Multipurpose prevention technologies (MPTs) delivered via mucoadhesive vaginal drug delivery systems offer a promising solution by simultaneously preventing multiple STIs, providing contraception and maintaining prolonged mucosal drug residence with reduced systemic exposure. This review comprehensively examines the scientific basis, design principles and formulation strategies for mucoadhesive vaginal systems including gels, films, wafers, tablets, rings and nanoparticle-based hybrids that tailored for STI prophylaxis and MPTs. Key considerations such as vaginal mucosal biology, microbiome preservation (particularly *Lactobacillus* dominance), resistance mitigation strategies, regulatory pathways, manufacturing challenges and evaluation methodologies are critically discussed. Despite significant advances, gaps persist in standardized testing protocols, predictive preclinical models incorporating commensal microbiota and longitudinal clinical data assessing repeated use safety and efficacy. This review emphasizes the need for microbiome-friendly excipients, PK/PD-driven formulation design, early regulatory engagement and user-centered development to optimize MPT performance. We conclude with practical recommendations and a proposed Phase I/IIa study design to advance clinically viable, patient-friendly mucoadhesive MPTs for comprehensive sexual and reproductive health protection.

Keywords: Mucoadhesive drug delivery, Multipurpose prevention technologies (MPTs), Vaginal drug delivery, STI prophylaxis, Vaginal microbiome, antimicrobial resistance.

1. Introduction

Sexually transmitted infections (STIs) are one of the major global public health challenges in present with more than >1 million of new infection reported everyday. The major reasons behind this includes high prevalence, frequent asymptomatic nature and serious long-term complications when not treated at time [1-2]. The STI transmitted globally because of unprotected sexual contact, with additional vertical transmission including contaminated blood products (probably reported in hospitals or laboratories), may occur during pregnancy, childbirth or breastfeeding. Most common sexually transmitted infections include chlamydia, gonorrhea, syphilis, trichomoniasis, genital herpes, human papillomavirus (HPV), hepatitis B or HIV [2-4]. In these, bacterial or parasitic infections often being curable or viral infections generally required long-term treatments. There is very few or even no symptoms for STI which results in delayed diagnosis and can increase the risk

of onward transmission, infertility, ectopic pregnancy, pelvic inflammatory disease, neonatal complications and heightened susceptibility to HIV [5].

STIs extends the burden on public health beyond acute infection. Non-treated or recurrent infections may lead to pelvic inflammatory disease, neonatal infections and enhance susceptibility to HIV acquisition and transmission. Long term treatment can result in drug resistances. The resistance of antimicrobial therapy particularly in pathogen such as *Neisseria gonorrhoeae* has further complicate treatment and slow the recovery rates. Dual therapy of antibiotics also implemented in treatment but not beneficial a lot because of further occurrence of resistance. New drugs like zoliflodacin, gepotidacin are being developed but are not yet a complete solution [3,6-7]. As a result, there must be need for innovative prophylactic approaches that are effective, acceptable and have capability to deliver broad-spectrum protections.

In recent years, the attention towards multipurpose prevention technologies (MTPs) have been gained as a promising approach to address multiple sexual and reproductive health needs through a single platform. The design of MTPs is in such manner that they can prevent more than one conditions simultaneously, so it can improve the convenience and potentially enhancing adherence. Among various dosage form for MTPs, mucoadhesive drug delivery systems are particularly considered more beneficial for vaginal prophylaxis because of its mucosal adherence which results in prolong drug residence with maintained therapeutic concentrations at the site of exposure. Such local drug delivery approach might reduce systemic exposure with enhancing efficacy and support the control release of drug from dosage form [8-10].

Integrity of antimicrobials, antiviral or contraceptives with mucoadhesive formulations can offers a rational strategy for STI prophylaxis. Such formulations can ensure protection against a broad range of pathogens while also addressing reproductive health needs in a single dosage form. This holds significant promise in improving prevention outcomes, especially in populations where adherence to conventional preventive measures is challengeable. Further research with such strategies is essential to optimize formulation performance, which can ensure safety and acceptability and validate these systems for clinically useful products [11-14].

This review focuses on the role of mucoadhesive drug delivery in STI prophylaxis, with particular emphasis on MPTs and combination formulations. It explores the scientific basis for localized

vaginal delivery with the advantages of multipurpose systems and the formulation challenges that must be overcome to develop effective and patient-friendly prophylactic technologies.

2. Mucosal biology and design principle for vaginal delivery

The vaginal mucosa is a hormonally responsive lactobacillus linked barrier that composed of stratified squamous epithelium covered by cervicovaginal mucus. The acidic nature, mucosal structure (Figure 1) and microbiome state of vaginal can strongly affects the drug diffusion, retention and safety. Such properties can favorable for the design of mucoadhesive/ mucopenetrating drug delivery systems. Non -keratinized stratified epithelium covered by cervicovaginal fluid rich in mucins, IgA or IgG, defensins, SLPI and other antimicrobials, forming a physical and biochemical barrier. In healthy women of reproductive age, the pH of vaginal fluid is varied from 4 to 5 which is composed of approximately 95% of water with 1-2% of negatively charged mucins. The thickness of mucus and secretion rate of vaginal fluid may vary with hormones or cycle. The presence of lactobacillus-dominated eubiosis can act as warrior to pathogens. High estrogen can develop glycogen-rich epithelium which in result increase the lactic acid production and low the pH [15-18].

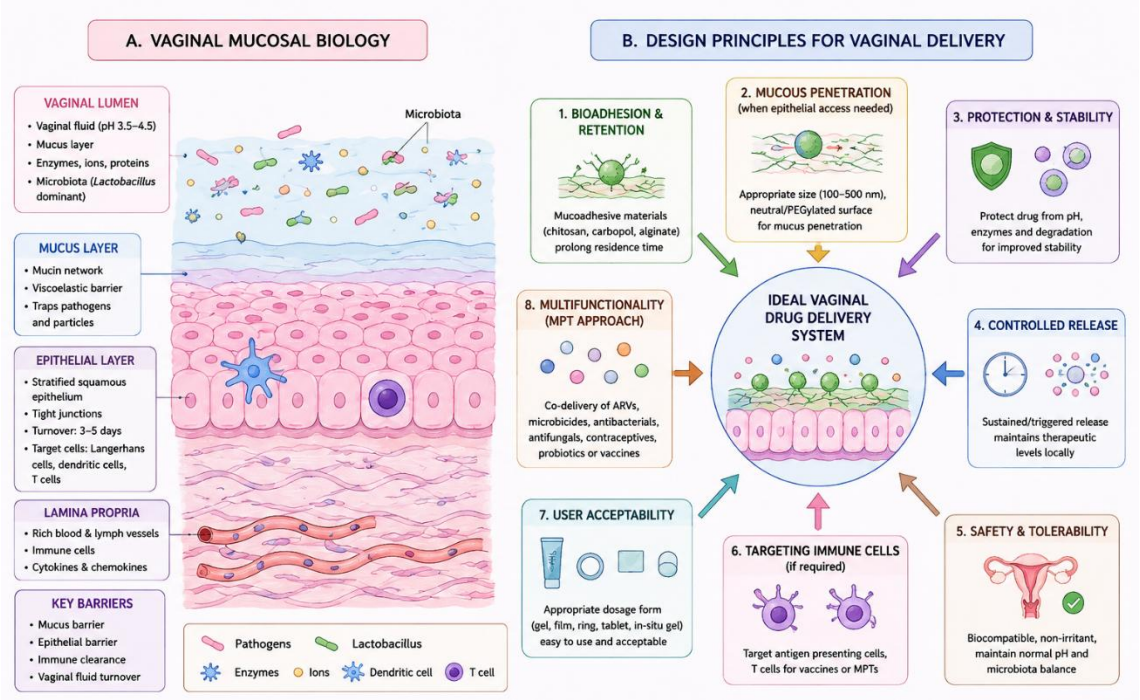

Figure 2: (A) Vaginal mucosal biology and (B) Design principles for vaginal delivery

Mucoadhesive systems are engineered to interact with mucus and epithelium to prolong residence and control release, while mucopenetrating systems aim to move through mucus without being trapped. Mucoadhesion based drug delivery is based on polymer chain length, its flexibility, functional groups present in chain, charge, hydration and cross-linking density. Hydrophilic mucoadhesive polymers are required for drug delivery include sodium alginate, gums (like guar, xanthan, karaya), pectin, chitosan, cellulose derivatives (HPMC), polyacrylic acids and thiolated polymers. For establishing intimate contact with mucus, mucoadhesive based drug delivery system must need surface properties including wetting, swelling, water absorption, contact angle and surface energy to establishing intimate contact with mucus [19-21].

Formulation strategies or site-specific tuning of drug delivery requires a high knowledge of local vaginal anatomy, its mucus secretion rate and turnovers, moisture or pH at the site. For better residence time or prolong release gels, thermogelling systems, tablets, films and nanoparticles used mucoadhesive or in-situ gelling polymers to resist clearance and maintain high local drug levels which can provide sustained release and precise cellular targeting, improving prophylactic and therapeutic efficacy [20,22-23].

3. Mucoadhesive vaginal drug delivery system for STI prophylaxis and MPTs

The main aim behind the mucoadhesive vaginal drug delivery system is to keep antivirals and antimicrobials at the mucosal surface to improve the local protection and drug release while limiting the systemic exposure of such drug agents (Figure 2). In STI prophylaxis and multipurpose prevention technologies (MPT), platforms need prolong retentions at site specific area with acceptable vaginal microenvironmental properties and capacity to carry single or combined active pharmaceutical ingredients over predetermined time for selective targets or disease conditions.

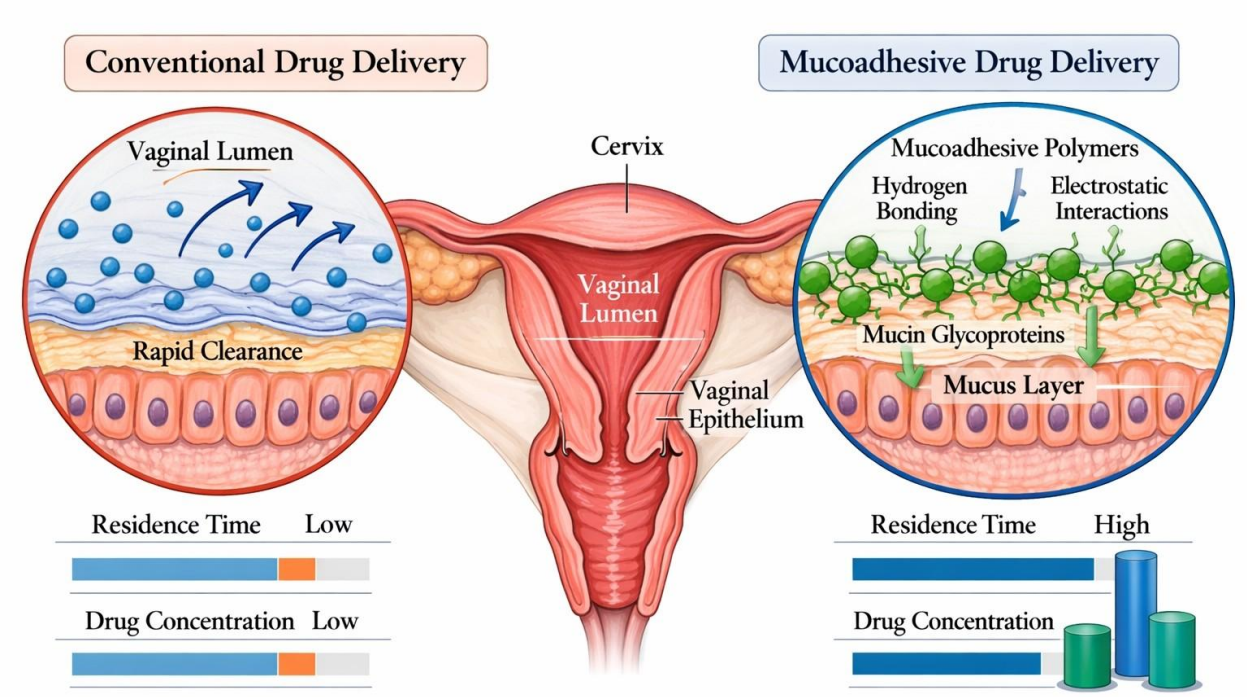

Figure 3: Comparative illustration between conventional and mucoadhesive vaginal drug delivery

3.1 Gels and in-situ gelling systems

Thermosensitive poloxamer-HPMC or Carbopol in-situ gels are designed as liquid preparations administration drug dosage forms that convert into semisolid gels when placed or applied at body temperature or after contact with vaginal fluid due to the pH or compositions of vaginal fluid that plays an important role in improving Spreadability at the time of application and prolong the retention time of drug dosage form at the site of application. The principle behind this formulation is to easy or human or patient compatible dosage form that applied in liquid form and at specific conditions it undergoes a sol-to-gel transition after insertion into vaginal cavity. Before become gel, the liquid can spread over a larger mucosal area in comparison to gel based formulations then after sol-to-gel transition can resist the leakage of liquid dosage form and rapid clearance. this dual behavior helps to overcome a common limitation of conventional gels or liquids-based dosage forms for vaginal drug delivery which may either drain quickly or fail to distribute uniformly [24,25].

Poloxamer 407, one of the thermosensitive component can be used in such sol-to-gel based dosage form because it acts as temperature dependent micellization and gelation. At room temperature it remains as pourable liquid and when applied at vaginal microenvironment it forms a more structure

gel network. Such properties attractive the poloxamer for vaginal drug delivery where residence time is important for local antifungal or antimicrobial or hormonal therapies [25,26].

HPMC also most commonly used polymer for its property that act as viscosity modifier and mucoadhesive enhancer in vaginal mucosal drug delivery system. It can strengthen the gel structure, improve the Spreadability of the dosage form and increase cohesiveness and controlled the drug release compared to poloxamer alone. So, HPMC complements poloxamer by improving mechanical integrity and help the gel to remain in contact with mucosa for a longer period for sustained and controlled release [24-26].

Also, Carbopol a strongly mucoadhesive and pH responsive component widely used in such sol-to-gel based formulation that can helps in increasing the resistance time of drug by improving adherence of gel to mucin and further it can control drug diffusion from the gel matrix. In vaginal drug delivery system, Carbopol can be especially useful because the acidic vaginal environment to supports formulation stability and loss the leakage and self-clearance of drug from dosage form [24-27].

3.2 Films, wafers, tablets, discs and rings

The main ideology behind the formulation of such mucoadhesive vaginal drug delivery systems including films, wafers, tablets, discs and rings were to developed a drug delivery system that overcome the poor retention, leakage and short residence time of conventional vaginal gels and pessaries by providing better site-specific drug delivery system for vaginal cavity with more reliable dosing and improved user convenience. Mucoadhesive solid or semi-solid vaginal dosage forms are designed to remain at the application site for longer than conventional formulations. The important of such drug delivery is because of low availability or retention time of conventional vaginal drug delivery system which can drain away, be diluted by vaginal fluids or be cleared by mucus turnover before enough drug is released to site specific. The mucoadhesive engineering behind the films, rings, wafers and tablets can results in prolonged contact, controlled release and more precise dosing which is especially useful for antifungals or HIV prevention agents [28,29].

Such systems are typically made from polymers such as HPMC, chitosan, pectin, gellan gum and related hydrophilic excipients that hydrate, swell and adhere to mucosa. Their advantages are practical as well pharmaceutical, as they are compact, portable, discreet and can be manufactured

to contain a single measured dose. For mucoadhesive vaginal drug delivery system, the unit-dose design helps more to improve reproducibility and reduces the variability often seen with conventional vaginal dosage forms. They can give action as adhesion + hydration + controlled diffusion rate as once it placed in vaginal cavity for mucosal drug delivery system [30].

Polymers are the one of the key ingredients in such formulations that make them best for mucoadhesive vaginal drug delivery systems. HPMC is one of the frequent use polymers for its flexible, swellable matrices and can improve retention time while pectin and gellan gum contributes to gelation, swelling and provides mechanical strength. Such combinations are often used for balance flexibility, adhesion, disintegration rate and release profile of drug and behaves more likely a quick-dissolving insets, for long residence adhesive matrix and to provide sustained release depot [28,30].

Freeze-dried HPMC vaginal discs are especially interesting because they can be engineered to carry both hydrophilic and lipophilic drugs in the same platform. Surfactants and hydroxypropyl-ß-cyclodextrin were used to co-loaded tenofovir and dapivirine, allowing formulation of a single disc with strong mucoadhesion and potential coitally dependent HIV protection [28].

Chitosan-pectin tablets are the good example of longer-acting adhesive design. These systems can sustain tenofovir release and maintain adhesion for upto 96 hours that make them attractive for coitally independent protection strategies. The key advantages in such mucoadhesive vaginal tables are that they form a hydrated polymer network that stays in contact with mucosal while sustainably release the drug from dosage form at controlled release [29-31].

Vaginal rings represent a separate long-acting category that has become central in HIV microbicide research. Unlike films or tablets, rings are designed to remain in the place for weeks or months and provide continuous release without daily user intervention. This is especially valuable where adherence is a major concern, because the device can maintain therapeutic levels over a long interval while minimizing the burden on the patient [30,32].

The literature supports the use of these systems for several local and preventive therapies which includes the antifungal agents like metronidazole, acyclovir and antiretroviral PrEP drugs. The HIV prevention delivery often described a clear progression from gels towards more user-friendly and adherence supportive systems such as rings or quick dissolve films, that progression reflects

the idea that formulation choose should match the real-life context of use, including timing of sex, acceptability, discretion and frequency of dosing. Mucoadhesive vaginal films, wafers, discs, tablets and rings provide a means of improving local retention (Table 1), dosing precision and release control in comparison with conventional dosage forms, with polymer systems based on HPMC, chitosan, pectin and gellan gum enabling formats ranging from on-demand quick dissolve products as long-acting mucoadhesive vaginal drug delivery systems [28-32].

Table 1: Comparative evaluation of mucoadhesive vaginal drug delivery system [28]

Drug delivery system	Advantages	Limitations	Pharmaceutical uses
Films	Thin, discreet, portable and easy to dose	May dissolve too quickly in some settings	In-demand local therapy or PrEP
Wafers/discs	High drug loading, prolonged contact, good mucoadhesion	Can be bulkier than films	Sustained local delivery, combination loading
Tablets	Precise unit dosing, controllable swelling and release	Needs careful design to avoid discomfort	Extended local release, coitally independent protection
Rings	Long-acting, low maintenance, adherence friendly	Less suitable for short-term or event driven use	Weeks to months prevention or maintenance therapy

3.3 Nano carriers and hybrid systems

Polymeric nanoparticles and nanogels have emerged as highly promising platforms for vaginal drug delivery because they can overcome the major physiological barriers of the vaginal environment, including mucus clearance, enzymatic degradation, limited epithelial permeability, and poor retention of conventional dosage forms. These systems are particularly being explored for intravaginal HIV pre-exposure prophylaxis (PrEP), antifungal therapy, and multipurpose prevention technologies (MPTs), where prolonged local drug delivery and targeted mucosal action are essential. Polymeric nanoparticles are colloidal carrier systems generally prepared from biodegradable polymers such as chitosan, poly (lactic-co-glycolic acid) (PLGA), alginate, polycaprolactone (PCL), Carbopol, and hyaluronic acid. These nanoparticles can encapsulate antiretroviral (ARV) drugs, antifungal agents, peptides, vaccines, and phytoconstituents, thereby protecting them from degradation and enhancing drug stability. Their nanoscale size allows better

interaction with the vaginal mucosa and facilitates penetration into epithelial tissues. Depending on surface modification, nanoparticles may exhibit either mucoadhesive or mucus-penetrating characteristics. Mucoadhesive nanoparticles are designed to strongly interact with mucin glycoproteins present in vaginal mucus. Polymers such as chitosan and Carbopol possess cationic groups that electrostatically bind to negatively charged mucosal surfaces, resulting in prolonged vaginal residence time. This prolonged retention improves local drug concentration and reduces dosing frequency. Mucoadhesive systems are particularly useful for sustained release applications and localized therapy against vaginal infections. However, excessive mucoadhesion may sometimes become a limitation because particles can become trapped within the outer mucus layer and fail to reach deeper epithelial tissues where viral transmission or infection occurs. To overcome this limitation, recent research has shifted toward mucus-penetrating nanoparticles. These systems are engineered with hydrophilic and neutrally charged surfaces, often through polyethylene glycol (PEG) coating or similar surface modifications, which minimize adhesive interactions with mucus fibers. As a result, polymeric nanoparticles and nanogels offer customizable surface chemistry that can enhance the mucoadhesive or mucus-penetration behavior and sustained release of vaginal drug delivery systems for antiretroviral. They are being integrated into gels, films, rings, microneedle and electro spun fibers for intravaginal HIV PrEP. Hydrogel-nanocomposite systems and mucoadhesive microsphere or microparticles are emphasized for long local residence with controlled release and potential vaccine or MPT applications. [33-36].

4. Multipurpose Prevention Technologies and Combine Therapies

Multipurpose prevention technologies are not just designed to “drug combinations” but it is a carefully designed systems where the choice of agents, release pattern, formulation and regulatory plan all have to work together for do more than one job at once. MPTs along with combination therapies is a planned work that usually performed to co-deliver two or more active pharmaceutical ingredients in one product to gets the broader protection within a single method. A common approach on this methodology indicates the pairing of contraceptive hormones with antiretroviral drugs to prevent pregnancy along with HIV at the same time within a single formulation, while other know formulations include combination of ARVs with antibacterial or antifungal agents to widen protection against multiple infections. The main outcomes from such combine therapies is

that it can improve adherence along with reduce the need for multiple products and better match real-world sexual and reproductive health needs [37,38].

The main idea for combination MPTs is the overlap between unintended pregnancy, HIV, and other STIs in women of reproductive ages. When a single product can address to a wide variety of risk is more practical over separate products for different risks especially in settings where access, privacy and consistent are used to be challenges. The goal behind such production is not only pharmacological efficacy, but also convenience, acceptability and sustained use [39,40].

Physicochemical compatibility between the active pharmaceutical ingredients in MPTs has some major challenges. The combination of two or more APIs can affect the solubility, stability, pH sensitivity, lipophilicity or degradation behavior of the ingredients which can results in loss of activity or poor product stability during the combination strategies. Another issue presents a challenge in formulation of MPTs is that each agent ma needs a different release profile in practical like a contraceptive component might require sustained release, while an antimicrobial might need faster local delivery to achieve protective concentrations. In such conditions if one drug release too fast and other too slow, the final product response may fail to protect against the one endpoint even if other is effective. Also, the MPTs are mostly intended for local use so the formulation must have to maintain at adequate tissue or mucosal drug delivery levels without causing irritation, tissue damage or loss of efficacy over time and should avoid disturbing protective flora, particularly lactobacilli in the vaginal environment as microbiome disruption can increase susceptibility to infection [40-43].

5. Evaluation methods in MPTs

In MPTs, the formulation of products the main goal is not only to measure the drug release kinetics or retention period of drug but the understanding of whether the product remain in place, release in controlled or sustained time period, preserve activity in the vaginal environment is also important. For such determinations, the evaluation of MPTs usually begins with *in-vitro* and *ex-vivo* tests are performed that useful for screening the formulation performance before its testing or evaluations on animals (*in-vivo studies*) and human studies. These evaluations are important as point of view for safety because these products are designed for local protection, so the evaluations strategies must reflect both pharmaceutical quality and biological relevance.

5.1 *In-vitro* testing

In-vitro testing is one of the most common testing procedures throughout the drug development which can used to study the mucoadhesion, drug release, gel behavior, drug safety and toxicity and formulation stability conder controlled laboratory conditions outside the living organisms. For the *in-vitro* evaluations of mucoadhesive formulations, one can often use tensile or adhesive strength assays, rotating-disk methods, rheological measurements, and shear-based tests to estimate how strongly a formulation interacts with mucosal surfaces. These evaluations can help to identify the bioavailability and biocompatibility of the formulations at specific site of application. Each evaluation has their own identification properties for the developed drug. The evaluation of tensile or adhesion strength of the formulation can help to identify the adhesion properties of formulation at mucosal tissue or mucin-coated surface. The time of adhesion at specific site can be evaluated using rotating-disk methods which provides an idea about the retention of drug under movement or fluid exposure. Rheological analysis is also one of the valuable evaluations for the determination of changes in viscosity and viscoelasticity for the formulation's behavior after application and whether it will spread, adhere or resist leakage.

Simulated fluid assay

The simulated vaginal fluid release assays are often combined with mucoadhesion studies to estimate that how much drug dose can be considered for bioavailability of drug from vaginal-like environment. The importance of such is because, a formulation might show strong adhesion but having too slow release of drug or rapidly release and having lower $t_{1/2}$ of drug. With the assay of simulated fluid, one can research the approximate hydration, dilution and dilution driven release that might occur after administration of vaginal drug dose. The best MPT candidates are those dosage forms that show a balance between retention and drug availability that drug dosage form adheres to mucosa for long enough that drug release active pharmaceutical agent to an effective level. This balance is central to local preventive systems because both underexposure and overexposure can be reducing performance or affect safety of drug and can cause toxicity or adverse drug reactions at higher or lower dose.

5.2 *Ex-vivo* testing

Ex-vivo studies use biological tissues that were taken from animals or human donors to provide a more realistic surface that artificial membranes. In vaginal drug delivery system, porcine vaginal tissue is often used for it resembles human tissue in structure and handling properties which makes it useful for adhesion and permeation experiments. A vertical "hung porcine vagina" protocol mimics leakage under gravity and distinguishes performance of mucoadhesive/colloidal systems from conventional formulations, with preserved mucosal histology, supporting its use as a physiologically closer *ex-vivo* model. Thermosensitive/mucoadhesive gels and nanoparticle-in-film systems for antiretrovirals were evaluated on ex vivo pig vaginal mucosa to confirm tissue adhesion, permeation control, and safety before *in-vivo* work. Similar *ex-vivo* mucosa models in the nasal route highlight advantages (retained native barrier, closer prediction than cell lines) but also variability from tissue thickness and species differences, underlining that these systems are bridge methods rather than definitive predictors. These tests can be measure whether a formulation can actually attach to mucosal tissue and how it behaves in a more biological meaningful setting. Shear-based *ex-vivo* tests are particularly helpful for studying the resistance of the formulation to displacement under force. They are more relevant than simple surface contact tests because they can simulate mechanical stress from movement, fluid flow and tissue deformation. Still *ex-vivo* systems cannot fully reproduce the living vaginal environment, so they should be viewed as bridge methods rather than complete predictors of clinical success [44-47].

One of the major problems in this field is that mucoadhesion methods are not standardized across laboratories. Different studies use different tissues, contact times, loading forces, temperature variations, instruments and calculation approaches which makes direct comparison of results difficult. Even small changes in experimental setup can alter the apparent adhesive strength or release behavior of a formulation. Standardized assays would improve cross-study comparison and make it easier to screen candidate formulations at an early stage. A common testing framework would ideally define the tissue source, surface preparation, fluid composition, temperature, contact time, force settings, and outcome measures. This would also help regulators and developers interpret data more consistently when evaluating MPTs for progression to advanced studies [44,48,49].

5.3 Animal and explant models

Animal models and tissue explant assays are widely used to evaluate tissue retention, distribution, safety and antiviral efficacy. Small-animal mucosal challenge systems can show whether a formulation reduces infection after exposure, while explant models allow researchers to study drug penetration and tissue-level responses in a controlled way. These systems are especially useful when the research question involves how the formulation behaves in real tissue rather than just how it performs in a tube or dish. Human vaginal tissue explants have been used to establish biosafety (no inflammation, immune activation or tissue damage) and prophylactic HIV-1 inhibition of candidate microbicides such as the G2-S16 dendrimer, supporting progression toward clinical trials. Macaque vaginal and rectal explant models allow ex vivo SHIV-RT/HSV-2 infection and show significant inhibition by microbicide gels such as MZC at nontoxic concentrations. A broader methods review on vaginal drug delivery describes organoids, fresh cervicovaginal mucus *ex-vivo* and tissue explants as intermediate, mechanistic platforms between *in-vitro* tests and *in-vivo* models. Explant assays also provide mechanistic insight into epithelial uptake, localized drug exposure, and tissue damage. Because they retain native architecture, they can be more informative than cell culture alone for understanding how MPTs interact with mucosal barriers. This makes them a valuable intermediate step between bench-top tests and human trials [50-52].

There are also some of limitation for animal models such like, although animal models are useful, they do not fully mimic human mucosal immunity, hormone-related changes or the vaginal microbiome. These differences can influence inflammation, susceptibility to infection, drug absorption and formulation retention. As a result, promising findings in animals do not always translate directly to humans. Non-human primate vaginal mucosa expresses key drug transporters at lower levels than human tissue, film-released antiretrovirals modulate transporter expression and may increase drug retention in macaques relative to humans, with implications for extrapolating efficacy and exposure [53,54].

6. Safety, Microbiome Preventions and Resistance Considerations in Mucoadhesive Vaginal Drug Delivery System

6.1 Safety and microbiome preservation

Preservation of a *Lactobacillus*-dominant vaginal microbiome and maintenance of the naturally low vaginal pH (3.8–4.5) are central safety objectives for mucoadhesive multi-purpose technologies (MPTs). The vaginal microbiota, primarily composed of *Lactobacillus crispatus*, *L.*

jensenii, *L. gasseri*, and *L. iners*, produces lactic acid that maintains acidic pH and prevents colonization by pathogenic organisms. Formulation components that disturb mucus rheology, increase osmolarity or possess broad-spectrum antimicrobial activity can deplete beneficial lactobacilli, compromise epithelial barrier function, and provoke local inflammation, thereby increasing susceptibility to sexually transmitted infections (STIs) and altering contraceptive efficacy. Excipient selection should prioritize near-physiologic tonicity, inertness toward representative *Lactobacillus* species and mucoadhesive polymers that adhere without denaturing mucins. Polymers such as chitosan, polycarbophil and hydroxypropyl methylcellulose (HPMC) have demonstrated favorable mucoadhesive properties, though their effects on commensal bacteria must be empirically validated. pH-buffering strategies can be useful but must avoid creating niches favorable to bacterial vaginosis (BV)-associated taxa such as *Gardnerella vaginalis*, *Prevotella bivia*, and *Atopobiumum*. Encapsulation approaches, targeted-release matrices and modular designs that spatially separate active pharmaceutical ingredients (APIs) from the mucosal surface can further reduce off-target microbial impacts. Preclinical safety assessment should combine *in vitro* co-culture assays (commensals and common pathogens), *ex-vivo* mucosal explants for epithelial integrity and cytokine profiling, mucus rheology testing, and simulated vaginal fluid release studies. Clinically, first-in-human and repeated-use studies must include longitudinal microbiome profiling (16S rRNA gene sequencing and where feasible, shotgun metagenomics), vaginal pH and Nugent scoring, mucosal immune markers (IL-1α, IL-8, SLPI) and stratification by sex-hormone status and behaviors that confound microbiota (antibiotic use, douching, sexual activity) [55-59].

6.2 Resistance risks and mitigation

Inclusion of antimicrobial agents or antiretrovirals in mucoadhesive MPTs raises the possibility of resistance selection if mucosal drug concentrations fall into sub-inhibitory ranges or exposure is intermittent. This concern is particularly relevant for vaginal fungal infections, where triazole-resistant *Candida* species have emerged, leading to empirical therapy failure and recurrent vulvovaginal candidiasis (RVVC). A recent study reported high resistance of *Candida* isolates from patients with RVVC to triazole antifungal agents, correlating with significant disruption of vaginal microecology. To mitigate resistance risk, formulations should be engineered for pharmacokinetic profiles that achieve and maintain inhibitory concentrations across the entire

exposed mucosal surface for the intended dosing interval, avoiding high initial bursts followed by prolonged low-concentration tails. Combining active agents with complementary mechanisms (e.g., azole combined with non-azole therapy or antifungal with potentiator such as ibuprofen or domiphen bromide) increases the barrier to resistance but necessitates rigorous PK/PD characterization to exclude antagonism. Preclinical resistance evaluation should include serial-passage assays under concentration gradients mimicking mucosal PK, determination of mutant prevention concentrations (MPCs) and *in-vitro* synergy/antagonism testing. Clinical trials should incorporate deep-sequencing surveillance for minority resistance variants and plan for post-marketing sentinel monitoring in high-use populations. For antiretrovirals (ARVs), favoring agents with high genetic barriers to resistance and low systemic exposure when systemic activity is unnecessary reduces broader selection pressure [60,61].

6.3 Regulatory and translational challenges

MPTs straddle regulatory categories, frequently presenting as drug-device combinations with multiple indications, which complicates pathway definition and evidentiary requirements. Regulatory pathways for MPTs are not fully established in many jurisdictions because products cross traditional regulatory categories (drug-device combinations, multiple indications). Developers should engage regulatory authorities early to agree on the product's primary mode of action, pivotal endpoints for each indication, acceptable surrogate markers and the necessary chemistry, manufacturing and controls (CMC) dossier elements. A staged evidence strategy. starting with local safety and tolerability, advancing through PK bridging and interaction studies for each API and culminating in indication-specific efficacy trials that helps de-risk development and clarifies labeling claims. Regulatory expectations may require separate contraceptive and STI-prevention efficacy demonstrations or well-justified combined endpoints; multi-arm development designs (API alone, contraceptive-alone, combined MPT) can deconvolute efficacy and safety signals while informing labeling [60-62].

6.4 Manufacturing and stability considerations

Co-formulating multiple APIs within mucoadhesive matrices presents chemical and physical compatibility challenges stress testing under relevant temperature and humidity profiles is essential to detect degradation, API-excipient interactions and physical instability (phase separation, crystallization). Hydrophilic films, wafers and hydrogels are particularly sensitive to ambient

humidity prevalent in many target geographies, making packaging, desiccants and humidity-resistant barrier films important considerations early in design. For products requiring sterility (implants, some devices), aseptic processing capabilities must be integrated at scale. Defining critical quality attributes mucoadhesive strength, mechanical integrity, API content uniformity, release kinetics and microbial bioburden guides process validation. Cost-effective manufacturing choices and technology transfer plans (e.g., modular or low-energy processes, local fill–finish partnerships) improve the likelihood of deployment in low-resource settings [63-65].

7. Gaps in the Literature and Research Priorities

The field lacks standardized, harmonized methods for measuring mucoadhesion, mucus interaction and physiologically relevant release under simulated vaginal conditions. This undermines cross-study comparability and translational confidence. A systematic review of mucoadhesive vaginal tablet testing identified heterogeneity in testing strategies, including polymer blends (46%), thiomers (18%), intermolecular complexes (18%), physical design (10%), micro-particulate technology (5%) and formulation technique (3%). Predictive preclinical models are limited, animal models frequently fail to recapitulate human vaginal microbiota and mucosal immunology and current *in-vitro* systems rarely include viable commensal communities. Priority translational work should emphasize development of *ex-vivo* human tissue models or organ-on-chip platforms that incorporate commensal lactobacilli, along with validated PK/PD models that translate mucosal concentrations to antimicrobial/antiviral efficacy and resistance risk. Clinically, there is an urgent need for Phase I/II trials of combination MPTs that integrate pharmacokinetics, safety, longitudinal microbiome, mucosal immunity and acceptability endpoints and for longitudinal cohort studies to assess repeated-use effects on microbiota composition, inflammation and STI incidence. Data sharing standards for microbiome and PK datasets would accelerate meta-analyses and hazard identification across platforms.

8. Practical Recommendations for Developers and Researchers

In early-stage screening prioritize excipients and matrices with demonstrated microbiome inertness and physiologic tonicity and perform accelerated humidity/temperature stability testing that mirrors target deployment settings. Adopt modular product architectures (nanoparticles or reservoirs embedded in a film or ring) to separate platform and API challenges and enable iterative optimization. Incorporate microbiome, pH and mucosal integrity endpoints into first-in-human

safety trials rather than relegating these assessments to later stages. Engage regulators early and use adaptive clinical designs where appropriate, plan dedicated interaction studies for contraceptive steroids and ARVs. Implement PK/PD driven design to minimize resistance selection and include resistance surveillance plans across clinical and post-marketed phases. Finally, integrate acceptability research from the outset to align form factor, dosing frequency and sensory attributes with end user preferences to maximize adherence and real-world effectiveness [66-69].

8.1 Concise Example Study Design

A pragmatic Phase I/IIa repeated use study can efficiently assess safety, microbiome effects, PK and acceptability. Enroll healthy, sexually active women with lactobacillus-dominant baselines into randomized arms placebo matrix and candidate MPT. Administer the product per intended real-world regimen for three months with monthly sampling and follow-up at 1 and 3 months post use. Primary outcomes should focus on local tolerability and mucosal integrity, secondary outcomes should include longitudinal microbiome profiling, vaginal pH, inflammatory cytokines, local/systemic PK and structured acceptability assessments. Embed exploratory deep sequencing for low-frequency resistance variants in relevant pathogens and stratify analyses by hormonal contraceptive use and menstrual cycle phase [62,70].

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