WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advances in Microbicides: *A Comprehensive Review*

[1]V. Mohanabaladevi, [2]Mr. S. Mohan Kumar

[1]B. Pharmacy, [2]B. Pharm., M. Pharm.
Pallavan Pharmacy College, Kolivakkam, Kanchipuram-631502

ABSTRACT:

STIs and other microbial pathogens can be prevented or their transmission reduced by using substances known as microbicides. Topical PrEp products including gels, capsules, pills, films, and intravaginal rings (IVR) are known as microbicides. The first microbicides were made as gels for everyday use, containing ingredients like acidifiers, surfactants, and monoclonal antibodies, but they didn't work well in clinical studies. Their historical evolution, modes of action, and most recent developments in formulation technologies are covered in this review. In addition, it discusses current clinical trials, related difficulties, and possible future paths, offering a thorough grasp of microbicides. We must admit that this method is insufficient for the successful development of microbicides, even though independent assessment of these components is required in some circumstances. An integrated clinical evaluation strategy must take each into account. The justification for this strategy is given in this article. This article is included in a special supplement that covers two presentations on clinical evaluation of microbicides from the "Recent Trends in Microbicide Formulations" symposium, which took place in Arlington, Virginia, on January 25 and 26, 2010.

KEY WORDS: Microbicides, clinical trials, acidifiers, surfactant

INTRODUCTION:

Microbicides are a preventive approach to controlling STIs, and they are especially important in the fight against HIV, bacterial vaginosis, and other infections. They can be applied either around the time of coitus or over an extended period of time. Originally, they were thought to be products that could provide broad protection against most STIs; they are applied directly to mucosal surfaces, providing localized protection, and they work by neutralizing or inhibiting harmful microbial pathogens before they can cause infection. These products were initially conceived as products that could offer broad protection against all most sexually transmitted infections. This review article covers the latest pharmaceutical developments in the area of microbicides dosage forms and delivery systems.

These products are primarily designed for use in the developing world and must therefore address cultural and societal issues generally unknown in the developed world. The first-generation microbicides evaluated clinically were primarily polyanions. Reverse transcriptase inhibitors of the second generation, including UC781, dapivirine, and Tenofovir, were created as intravaginal rings (IVRs) and gel formulations. Additional dosage forms in development include tablets/capsules, fast-dissolving films, and maybe vaginal sponges. Microbicides are becoming increasingly feasible for widespread use in public health initiatives as a result of continuing research.

CLASSIFICATION OF MICROBICIDES:

Based on their evolution and specificity:

- **First-generation microbicides:** These are non-specific agents, such as detergents, which broadly target microbes but may cause irritation. The first-generation microbicides evaluated clinically were principally polyanionsThese drugs, administered as intravaginal gels, were found to be ineffective in preventing transmission of HIV from men to women.
- **Second-generation microbicides:** Second-generation drugs such as Tenofovir, dapivirine, and UC781 are reverse transcriptase inhibitors developed as gels formulations and intravaginal rings (IVRs).These focus on specific targets, such as viral entry inhibitors, reducing side effects and increasing efficiency.
- **Third-generation microbicides:** These include drug-loaded Nanocarriers and combination products, which improve stability, release kinetics, and overall effectiveness.

Based on mode of action :

A. Nonspecific microbicides:

i. **Surfactants and detergents**: The first-generation microbicides were nonspecific substances that directly inactivated bacterial and viral STIs. They included detergents (like sodium dodecyl sulfate) and surfactants (like nonoxynol-9). These nonionic surfactants denature the membrane proteins of sexually transmitted infections and disintegrate their lipid sheath. Because of their short therapeutic window, possibility for vaginal inflammation, and elevated risk of HIV acquisition during phase II and phase III clinical trials, Nonoxynol-9 and Savvy are not good choices for microbicides.

ii. **Acid buffering agent**s: A second category of nonspecific first-generation microbicides includes acid-buffering agents. Products like BufferGel® and ACIDFORM are formulated to sustain the vagina's naturally low antimicrobial pH (ranging from 3.5 to 4.5), even in the presence of semen, which temporarily raises vaginal pH to a neutral level. By doing so, they reduce the risk of infection by acid-sensitive pathogens such as HIV and other sexually transmitted infections. While both BufferGel® and ACIDFORM (also known as Amphora) aim to maintain vaginal acidity and prevent HIV transmission, clinical trials did not demonstrate the effectiveness of BufferGel®.

B. Moderately specific microbicides:

9. **Linear polyanions:** Macromolecular linear anionic polymers, such as cellulose sulphate (Usher Cell), carrageenan (Carraguard), PRO 2000, and cellulose acetate phthalate (CAP), are the primary constituents of the moderately selective microbicide class. These substances are effective against a wide range of infections. However, in clinical trials, they have shown poor efficacy, with Carraguard failing to stop HIV transmission.

10. **Dentrimers:** Using HIV isolate, the Dentrimers SPL7013 is a unique synthetic macromolecule with comparable effectiveness against CCR5 and CXCR4. Star Pharma PTV Ltd created the vaginal microbial 3% SPL7014 Gel (VivaGelR) to prevent HSV and HIV infections. In vitro and animal models have shown their effectiveness against HIV and HSV.

Anti-retroviral based microbicides:

1) Anti-retroviral agents are the drugs or medications that treats HIV by stopping the virus from replication

2) Tenofovir Gel: Tenofovir, a nucleotide reverse-transcriptase inhibitor, is widely used in its oral formulation for the treatment of human immunodeficiency.

3) Some of the anti-retroviral agents are give below in table,

S.NO	Mechanism of action	Drugs
1.	Entry inhibitors or FIs	Enfuvirtide, maraviroc
2.	NRTIS	Tenofovir, adefovir, zidovudine, didanosine, stavudine, emtricitabine, abacavir, lamivudine
3.	NNRTIS	Efavirenz, rilpivirine, nevirapine, dapivirine or etravirine
4.	PIs	Ritonavir, darunavir
5.	IIs	Dolutegravir, raltegravir

Abbreviations: FIs- Fusion Inhibitors , NRTIs-Nucleoside Reverse Transcriptase Inhibitors, NNRTIs-Non-nucleoside Reverse Transcriptase Inhibitors, PIs- Protease Inhibitors, IIs -Integrase Inhibitors.

MECHANISM OF ACTION:

Microbicides prevent HIV and other sexually transmitted infections (STIs) by

- Disrupting Pathogen Membranes
- Creating Barriers
- Inhibiting Viral Entry
- Preventing Viral Replication.
- Boosting Mucosal Immunity
- Reverse Transcriptase Inhibitors
- Entry Inhibitors
- Broad Spectrum Activity

Here's a more detailed explanation of the mechanisms of action of microbicides:

a. **Disrupting Pathogen Membranes:** Some microbicides, like surfactants, damage the lipid membranes of pathogens, leading to their inactivation.

b. **Creating Barriers:** Certain microbicides form a physical barrier between the pathogen and vaginal tissues, preventing infection.

c. **Inhibiting Viral Entry:** Some microbicides prevent pathogens from entering target cells by interfering with viral attachment or fusion.

d. **Preventing Viral Replication:** Microbicides can interfere with viral replication by targeting enzymes or other processes essential for viral reproduction.

e. **Boosting Mucosal Immunity:** Some microbicides can enhance the body's natural defenses in the vaginal mucosa, making it more resistant to infection.

f. **Reverse Transcriptase Inhibitors:** Many microbicides in clinical development are reverse transcriptase (RT) inhibitors, which target a critical enzyme needed for HIV-1 to convert viral RNA into DNA.

g. **Entry Inhibitors:** Other microbicides target specific viral-host cell interactions, preventing HIV from entering cells.

h. **Broad Spectrum Activity:** Microbicides are developed to provide broad-spectrum protection against various pathogens, and researchers can modify active ingredients to enhance their effectiveness.

Examples:

-Tenofovir gel: One proven microbicide that protects against HIV, with subpopulation analyses showing trends towards effectiveness against other STIs.

-Surfactants and acidifying agents: The initial microbicide agents function non-specifically by breaking down viral and cellular membranes or by establishing an unfavorable environment for pathogens.

-Small-molecule drugs: Bind to gp120 and prevent subsequent conformational changes, inhibiting infection.

- Surfactants: These agents, such as Nonoxynol-9, disrupt microbial membranes, leading to pathogen destruction.

- Polyanionic compounds: They block viral entry by preventing viral attachment to host cells, as seen with Carrageenan.

- Antiretroviral-based microbicides: Such as Tenofovir gel, these microbicides inhibit viral replication, effectively preventing HIV infection.

- Broad-spectrum antimicrobial: Agents like silver nanoparticles target multiple pathogens, making them highly effective against a wide range of infections.

RECENT ADVANCE IN MICROBICIDE FORMULATIONS:

Innovations in formulation technology have enhanced microbicide performance:

- **Nanotechnology-based delivery systems:** Liposomes, dendrimers, and polymeric nanoparticles enhance drug stability and enable controlled release.
- **Hydrogel-based formulations:**These provide extended retention and regulated drug delivery, minimizing the frequency of application.
- **Intravaginal rings:** These devices ensure sustained drug release over extended periods, enhancing protection and compliance.
- **Combination therapy microbicides:** By integrating multiple active agents, these formulations target multiple infection pathways simultaneously.

CLINICAL TRIALS AND EFFICACY STUDIES:

Several clinical trials have assessed the effectiveness of microbicides:

- The CAPRISA 004 study on Tenofovir gel demonstrated a 39% reduction in HIV infection rates among participants.
- The FACTS 001 study provided insights into user adherence and acceptability, highlighting key challenges in real-world applications.
- Ongoing trials are investigating dapivirine rings and Griffithsin-based formulations, aiming to improve efficacy and user compliance.
- Preclinical and early-stage clinical development is underway for a number of combination medications that have the potential to advance to further stages of clinical trials. Classifying these medications based on their hormonal classification would be simpler for us. Hormonal-type medications usually include a hormonal contraceptive (LNG, EE, Etonogestrel, or Norelgestromin) along with a variety of antiretroviral medications, such as DPV, TDF, TFV, or Islatravir and Capegravir. These combinations, as previously stated, work to stop ovulation and stop HIV from replicating.

- Combining contraceptive hormones with QGRFT, a stable analog of non-anti-retroviral anti-HIV lectins that binds to the HIV envelope glycoprotein and blocks entry into target cells, is another example of possible hormonal medications. The main goal of non-hormonal microbicides made up of several ingredients is to bind or inactivate sperm in order to stop HIV transmission and conception. Some are based on combining antiretroviral medications, notably TDF, with agglutinating sperm antibodies or monoclonal antibodies, such as mAb 2C7, which causes the killing of Neisseria gonorrhoeae.
- Monoclonal antibodies are not the only option for future use; IVR, which contains a fully human antibody (HCA) that can agglutinate sperm and is integrated into a sustained release delivery system, effectively prevents both pregnancy and the spread of HIV. In the presence of semen, additional medication combinations, such as QGRFT with organic acids packaged as fast-dissolving inserts, lower vaginal pH and make it inactive. Combinations of polyphenylene and carboxymethylene (PPCM) are further potential medications that can make semen infertile without damaging other cells. By inhibiting hyaluronidase and causing premature acrosome loss in sperm, PPCM stops sperm from fertilizing an ovum.
- Some products have been released using innovative delivery mechanisms, with the exception of new pairings with well-known ones. In order to get greater concentrations of both medications in the genitalia than would be possible with their distribution in a liquid carrier, TFV/EFV nanoparticles (NPs) are incorporated onto a polymer film basis (TFV/EFV NPs in film). With their innovative features, the combination microbicides covered here have bright futures. Notably, these formulations are approaching commercial viability and are in a variety of clinical trial stages, from early to advanced phases. Microbicides have the potential to be used in future preventive applications, as evidenced by the large number of candidates undergoing clinical evaluation.

CHALLENGES AND LIMITATIONS:

Despite progress, microbicide development faces several challenges:

1. **User adherence and acceptability:** Regular and correct application remains a challenge for many users.
2. **Drug resistance development:** Prolonged use of microbicides may contribute to microbial resistance, reducing their long-term effectiveness.
3. **Cost and accessibility:** Affordability and distribution in low-resource settings remain significant barriers.
4. **Regulatory and ethical considerations:** Clinical approvals and public health policies must balance safety, efficacy, and accessibility.

FUTURE PROSPECTS:

Several promising research areas are shaping the future of microbicides:

- **Gene-editing-based microbicides:** CRISPR technology is being explored for precise microbial eradication.
- **Probiotic-based microbicides:** Utilizing beneficial bacteria to outcompete harmful pathogens presents a natural, sustainable approach.
- **Next-generation Nanocarriers:** Smart polymers and stimuli-responsive delivery systems aim to enhance drug effectiveness.
- **Policy and advocacy efforts:** Increased funding, public health initiatives, and policy support are crucial for widespread adoption and impact.

CONCLUSION:

One of the significant development in STI prevention is microbicides. Even though there has been a lot of improvement, future studies should concentrate on developing novel delivery systems, enhancing adherence, and increasing accessibility worldwide. Microbicides have the potential to significantly lower the global STI burden with sustained efforts.

REFERENCE:

1. Abdool Karim, Q., Abdool Karim, S.S., Frohlich, J.A., Grobler, A.C., Baxter, C., Mansoor, L.E., Kharsany, A.B.M., Sibeko, S., Mlisana, K.P., Omar, Z., Gengiah, T.N., Maarschalk, S., Arulappan, N., Mlotshwa, M., Morris, L., Taylor, D., CAPRISA 004 Trial Group, 2010. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 329, 1168 1174.
2. Adams, J.L., Kashuba, A.D.M., 2012. Formulation, pharmacokinetics and pharmacodynamics of topical microbicides. Best Pract. Res. Clin. Obstet. Gynaecol. 26, 451–462.
3. Ari n, K.K., Venkatraj, M., Michiels, J., Joossens, J., Vereecken, K., Van der Veken, P., Abdellati, S., Cuylaerts, V., Crucitti, T., Heyndrickx, L., Heeres, J., Augustyns, K., Lewi, P.J., Vanham, G., 2013. Diaryltriazine non-nucleoside reverse transcriptase inhibitors are potent candidates for pre-exposure prophylaxis in the prevention of sexual HIV transmission. J. Antimicrob. Chemother. 68, 2038–2047.
4. Ayehunie, S., Cannon, C., Lamore, S., Kubilus, J., Anderson, D.J., Pudney, J., Klausner, M., 2006. Organotypic human vaginal-ectocervical tissue model for irritation studies of spermicides, microbicides, and feminine-care products. Toxicol. In Vitro 20, 689–698.

5. Clark, M.R., Friend, D.R., 2012. Pharmacokinetics and topical vaginal effects of two tenofovir gels in rabbits. AIDS Res. Hum. Retroviruses 28, 1458–1466. Dahl, T., He, G.X., Samuels, G., 1998. Effect of hydrogen peroxide on the viscosity of a hydroxyethylcellulose-based gel. Pharm. Res. 15, 1137–1140.

6. Dezzutti, C.S., Rohan, L.C., Wang, L., Uranker, K., Shetler, C., Cost, M., Lynam, J.D., Friend, D., 2012. Reformulated tenofovir gel for use as a dual compartment microbicide. J. Antimicrob. Chemother. 67, 2139–2142.

7. Braun KE, Boyer JD, Henderson MH, Katz DF, Wax A. Label-free measurement of microbicidal gel thickness using low-coherence interferometry. J Biomed Opt 2006;11:20504.

8. Carballo-Dieguez A, Balan IC, Morrow K, Rosen R, Mantell JE, Gai F, Hoffman S, Maslankowski L, El-Sadr W, Mayer K. Acceptability of tenofovir gel as a vaginal microbicide by US male participants in a phase I clinical trial (HPTN 050). AIDS Care 2007;19:1026–31. [PubMed: 17852000]

9. Coggins C, Blanchard K, Alvarez F, Brache V, Weisberg E, Kilmarx PH, Lacarra M, Massai R, Mishell D Jr, Salvatierra A, Witwatwongwana P, Elias C, Ellertson C. Preliminary safety and acceptability of a carrageenan gel for possible use as a vaginal microbicide. Sex Transm Infect 2000;76:480–483. [PubMed: 11221133]