

Formulation Challenges and Emerging Delivery Systems in Vaginal Microbicide Research

Dr. Mrs. Sudha Rathod⁽¹⁾, Ms. Anjali Rai⁽²⁾, Mr. Karan K. Singh^(3*), Ms. Khushi B. Chaubey⁽⁴⁾, Ms. Pallavi B. Hase⁽⁵⁾.

(1) Principal, Oriental College of Pharmacy

(2) Assistant Professor, Oriental College of Pharmacy

(3) , (4), (5) Research Scholar, Oriental College of Pharmacy

Corresponding Author: Mr. Karan Krishnakumar Singh, Research Scholar, Oriental College of Pharmacy, +91 8104923327.

Date of Submission: 25-01-2026

Date of Acceptance: 05-02-2026

ABSTRACT:

The use of vaginal microbicides to control STD transmission from men to women has received a great deal of attention. The purpose of this review article is to highlight the history of developing vaginal microbicides and review the development of early vaginal microbicide formulations, clinical efficacy failures, and lessons learned from these clinical outcomes. The original vaginal microbicide candidates (surfactants, polyanions, acidifying agents) had in vitro antiviral activity but had limited clinical effectiveness due to poor adherence, mucosal irritation, disruption of the vaginal microbial flora, and limited efficacy. The challenges faced by these products were due in part to the complexity of the vaginal environment and the need for physiological compatibility between microbicide formulation and the vaginal microenvironment.

This review further identifies advances in understanding STD transmission and the pathophysiology of the vaginal immune system, which have led to the development of new antiretroviral-based vaginal microbicides that have greater specificity and potency. New drug delivery methods, including gels, vaginal rings, films, nanoparticles, and combination systems, are also reviewed as means by which to improve the retention of vaginal microbicides, achieve sustained drug release, and improve adherence. The conclusion provides an overview of future directions in terms of developing multipurpose prevention technologies, and user-friendly formulation design for vaginal microbicides, which give renewed hope for effective vaginal microbicides for STD prevention.

Keywords: Vaginal, Nanoemulsion, Nanoemulgel, Immunity, Infection, Techniques, Challenges, Strategies, Regulatory, Market

I. INTRODUCTION:

Human Vagina:

Contrary to the belief that the vagina has a linear canal extending directly up to the sacral promontory, its actual structure is more complex. Many medical illustrations and educational materials oversimplify the structure, giving the misleading impression that objects inserted into the vagina could easily fall out.

It extends from the cervix of the uterus and has been primarily studied through cadaver dissections and imaging techniques.

It shows a curved configuration: a narrower, bell-shaped downward portion, a wider, nearly plane upward section.

Thus, it starts from the pelvic cavity, passes through the pelvic and urogenital diaphragms. The bulbocavernosus muscle, pubococcygeus muscle function as sphincters at the vaginal opening. The surface of the vaginal wall contains rugae—fold that provide elasticity, structure support, and greater area.

It has a rich vascular network supplied by branches of the inner iliac, uterine, middle rectal, and inner pudendal arteries. Venous leakage primarily occurs from the inner iliac veins, bypassing first-pass metabolism, although some drainage also occurs via the hemorrhoidal veins. Lymphatic channels are abundant, and innervation is provided by the pudendal nerve along with fibers from the inferior hypogastric and uterovaginal plexuses.

Although they themselves lack glands, they produce fluid from cervical secretions, plasma transudation, cellular shedding, with contributions from fallopian tubes and endometrium. Women of reproductive age secrete about 3–4 g of fluid every four hours, postmenopausal secretion drops by roughly 50%. Vaginal fluid contains a variety of

biological components, including proteins, carbohydrates, enzymes, etc. Sexual activity would influence the amount of such secretions.

The pH maintained between (3.8-4.2), primarily due to production of lactic acid produced by *Lactobacillus*

species that metabolizes the glycogen. However, they rise during menstruation, after intercourse, as semen, vaginal transudate are alkaline. Additionally, an epithelium contains enzymes that would influence stability, effectiveness of drug formulations intended for such administration.

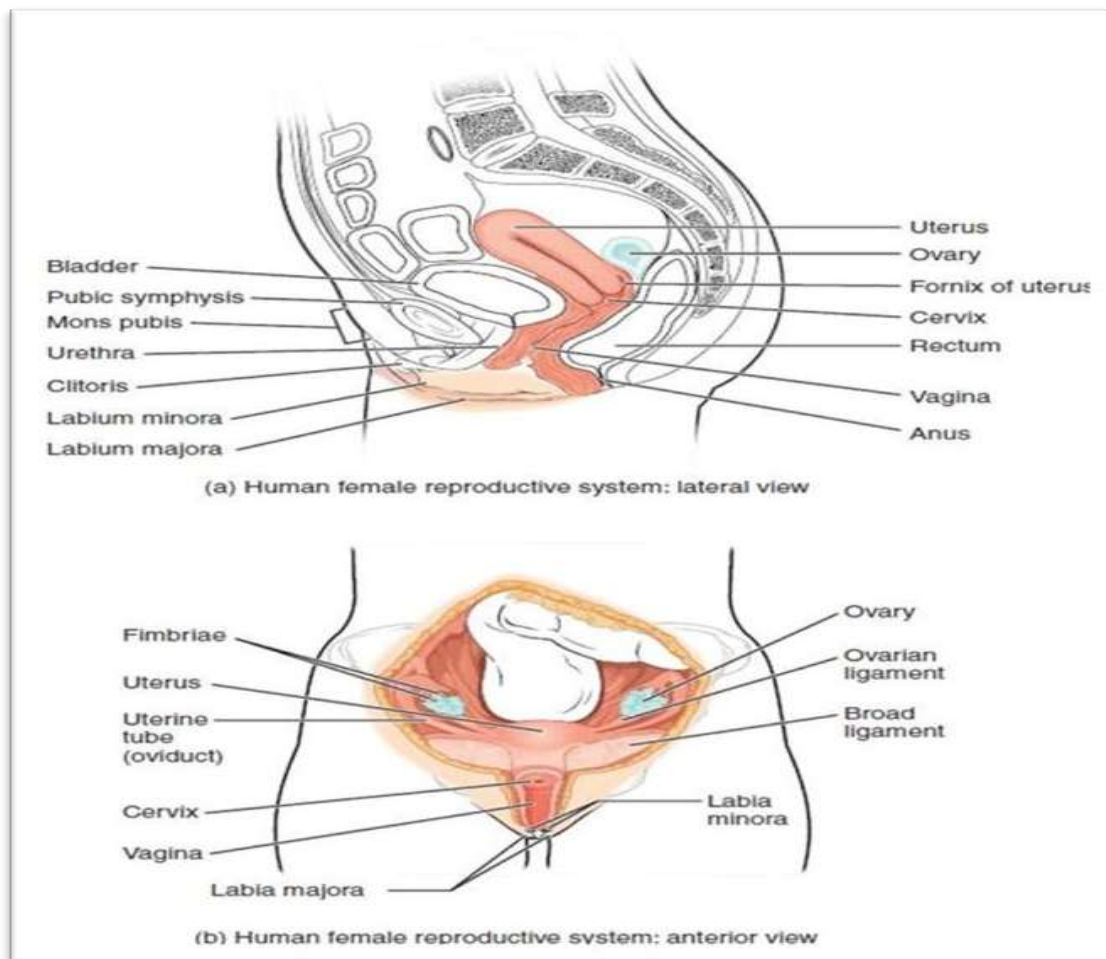


Figure 1: Lateral and Anterior view of Women's Genital System

Drug Delivery through vagina: It is a considerable administration for therapeutic, pharmaceutical fields, especially in female's health. It is a conventional approach, considering devices (such as pessaries, gels, suppositories, rings) attempt not to offer just a localised activity but also longer therapeutic levels through medication reaches the systemic circulation [12]. Low daily dosages and longer release of drug made possible through vaginal administration. They provide several unique advantages, challenges, needs as compared to other delivery methods.

Advantages:

- Non-invasive and Self-administered
- No First-Pass Metabolism
- Avoidance of Gastrointestinal Problems
- Potential for therapeutic activity
- Rich Blood Supply

Challenges:

- Anatomical and Physiological Barriers
- Limited Drug Retention and Absorption

- Interindividual Variability
- Formulation Challenges
- Patient Compliance and Acceptance
- Stability and Storage Issues

Needs:

- Achieved Pre-determined & Prolong Release
- Enhance Drug Retention & Bioavailability
- To Cross Epithelial Barriers
- Minimize Side Effects

NANOEMULSIONS

Nanoemulsions are special tiny particles that carry medicine. It is really small, having size from 10-1,000 nanometers. These are solid balls,

their region is not organized with a natural oily feel. They could be made by using magnetic particles which help to produce medicine at the right place in the body. As a way to transport medicine, they provide benefits with no unwanted harmful reactions.

"Nanoemulsion" can also mean a miniemulsion, which is a mixture of water and oil which stays stable because a layer is formed which is soap-like substances on the region. Particle size between 100-400 nm. Since, it is so small, it looks clear. Three main classes of nanoemulsions:

- (a) O/W,
- (b) W/O,
- (c) bi-continuous, mix of both that is W/O/W, O/W/O

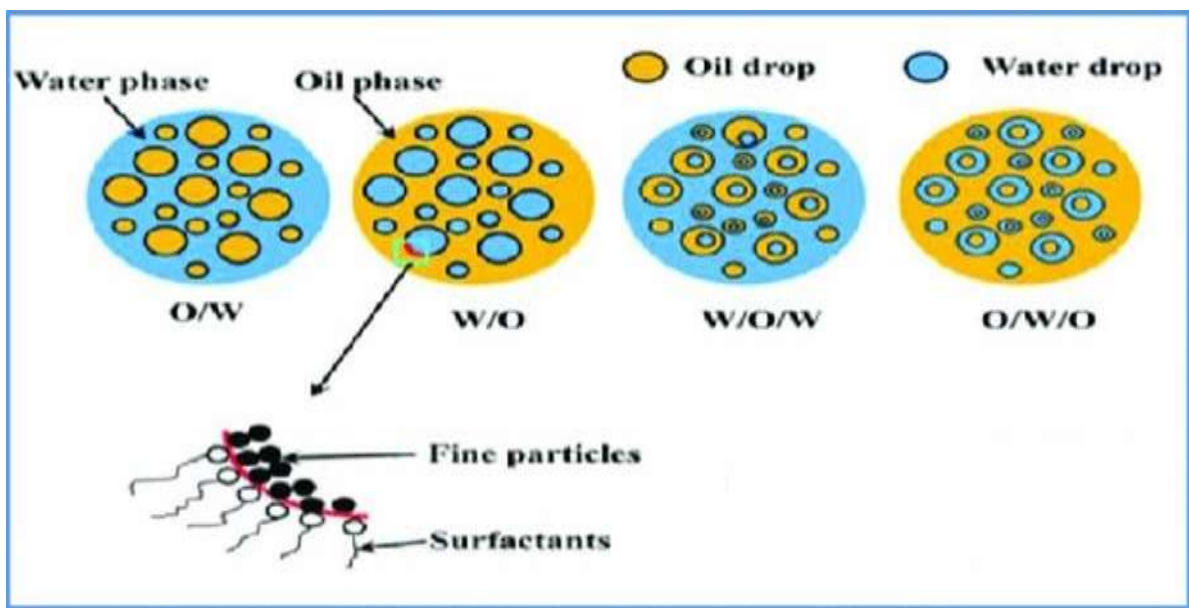


Fig. 2: Class of Nanoemulsions

Advantages:

- Improved Absorption of lipophilic, lipophobic drugs
- Mucoadhesive Properties
- Minimal Irritation
- Physical, Thermodynamic Stability
- Targeted, Localized Delivery
- Substitute for Nanoparticles and others
- Less amount of energy is required

Components:

Table 1: Components

Components	Function	Examples
Oil Part	To Solubilize lipophilic drugs	Soybean oil, Oleic acid, Isopropyl myristate, Tea tree oil, etc
Aqueous Part	Disperses system, To dissolve hydrophilic drugs	Water, Buffers, etc
Surfactants	Reduce interfacial tension	Tween 80, Span 20, Lecithin, etc
Co-surfactants	Enhance emulsification, stabilize droplets	Ethanol, PEG, etc
API	Therapeutic effect	Hormones, Antivirals, Antifungals, etc
Additives	Stability, adhesion, comfort	Chitosan, citric acid, preservatives, etc

Methods To Prepare:

1. High-Energy Emulsification Techniques:

This technique uses a lot of energy to make nanoemulsions.

- **Ultrasonication Method:** This involves a good way making the droplet really small. This process using a device known sonicator probe. Probe contains crystals made up of piezoelectric quartz. When electric current passed through it, migrate back, forth. When tip of sonicator touches liquid, they may produce vibrations, triggers cavitation. It is produced when tiny bubble of gas collapse in solution. Which helps to form an emulsion. It is mostly used for making particle size around 0.3 micrometers.
- **High-Pressure Homogenization Method:** To prepare nanoemulsions, high-pressure homogenization method used. This method uses a machine namely high-pressure homogenizer. It helps for preparation of an emulsion with tiny particles, less than 1 nanometer.

2. Low Energy Emulsification Techniques:

- **Phase Inversion Temperature (PIT) Methods:** This method uses temperature to alter phases of

microemulsion.

- **Spontaneous Emulsification Method:** This contains three steps.

First, an oil is mixed with one type of surfactant (lipophilic) in a water-miscible solvent along with another type of surfactant (hydrophilic). Then, this intermediate is added to an aqueous solution while mixing it continuously with a magnetic stirrer, which makes an o/w emulsion. Finally, the water is removed by heating the resultant under lower pressure.

EMULGELS

EMULGELS: It is a clear, stable liquid that combines water, oil, a surfactant, and a suitable gelling agent. It looks the same from any angle because it is optically identical in all directions. These systems have less surface tension, allow them to spread easily over skin, even get into tiny areas like wrinkles, tiny gaps. This helps the medicine move more effectively through the skin. When a gel and an emulsion are combined in a single product, it is called an emulgel.

It is considered a promising way to transport medicine within it because they show dual release mechanism via firstly, through the gel matrix. Secondly, from an emulsion. Achieving the main goal, hydrophobic drugs are delivered directly within

bloodstream through skin.

Benefit of Emulgels:

- Avoiding first pass metabolism.
- High selectivity to a targeted site.
- Enhance stability.

- Improved drug loading capacity.

Category of Emulgels:

a. Depending upon emulsion type: As shown in Figure 3.



Figure 3. Depending upon emulsion type

b. Depending upon droplet size: As shown in Figure 4.

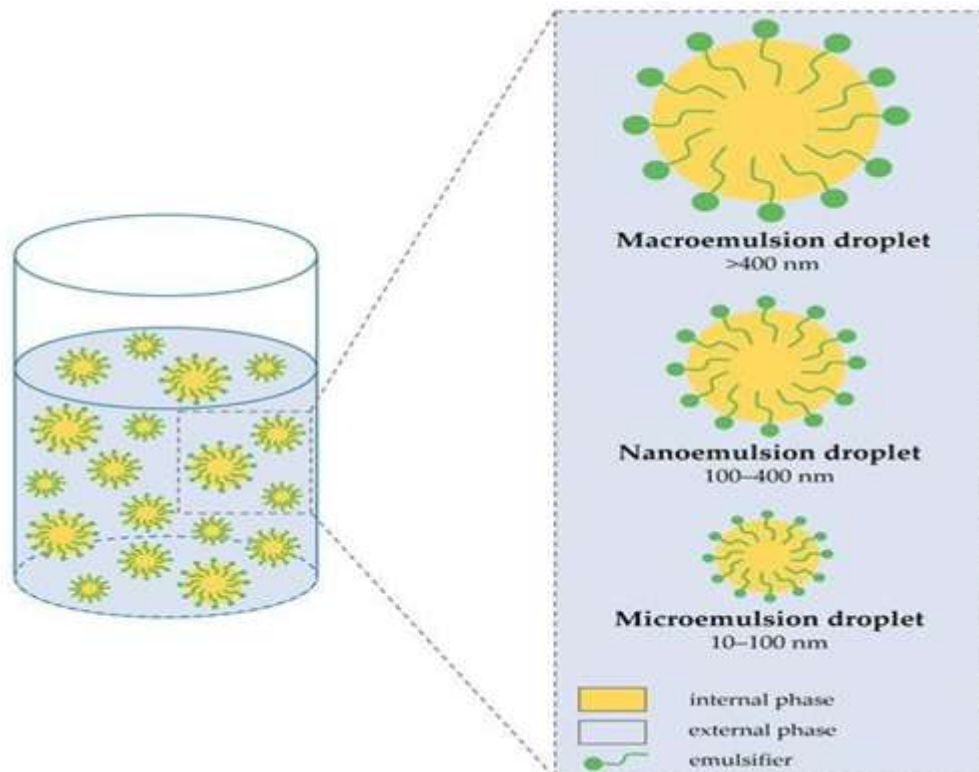


Figure 4. Depending upon droplet size

Emulgel role via Vaginal Drug Delivery:

- 1) **Enhanced delivery of drug:** Offers dual-releases how that can control the rate at which the released drug into the vaginal environment.
- 2) **Enhanced stability, shelf life:** The Oil part of an emulsion can safeguard drug from enzymatic degradation of vaginal environment, ensuring drug remains safe for longer period.
- 3) **Easy application:** They are generally easy for use and spread, leading better patient compliance and adherence.
- 4) **Other Specific application:** It could be used for delivery of antifungal, antibacterial drugs to treat various infections. Also helps to deliver contraceptive substances for localized action.
- 5) **Research and development:** Emulgels are considered a promising area of research for developing innovative drug delivery systems.

Common Gelling Agents in Emulgels: As shown in Table 2.

Table 2. Common Gelling Agents

Gelling Agent	Type	Properties	Sensitivity
Carbopol 934/940/980	Synthetic polymer	High viscosity, clear gel, stable	pH-sensitive
HPMC (Hydroxypropylmethylcellulose)	Semi-synthetic cellulose	Form smooth gels, good film-forming ability	Mildly pH-sensitive
Sodium Alginate	Natural polysaccharide	Form gel in the presence of calcium ions	Sensitive to ions
Poloxamer 407 (Pluronic F127)	Synthetic block copolymer	Thermo-reversible gel (liquid when cold, gel at body temperature)	Temperature-sensitive
Guar Gum	Natural polysaccharide	Biodegradable, thickening and stabilizing agent	pH stable

NANOEMULGEL SYSTEMS

NANOEMULGEL: When nanoemulsion is added to a gel, nanoemulgel is formed. The nanoemulsions is clear formulation that stays safe over time. They kept safe by forming a thin layer with the use of molecules of co-surfactant, surfactant. Particles in nanoemulsions are very small, < 400 nanometers in size. This improve way of drugs pass through skin both in lab tests and in real-world situations. The nanoemulsions are better

in helping drugs move through the layers of skin as compared to traditional topical treatments like regular gels and emulsions.

Procedure for making a nanoemulgel:

As shown in Figure 5. Represent the procedure for making a nanoemulgel.

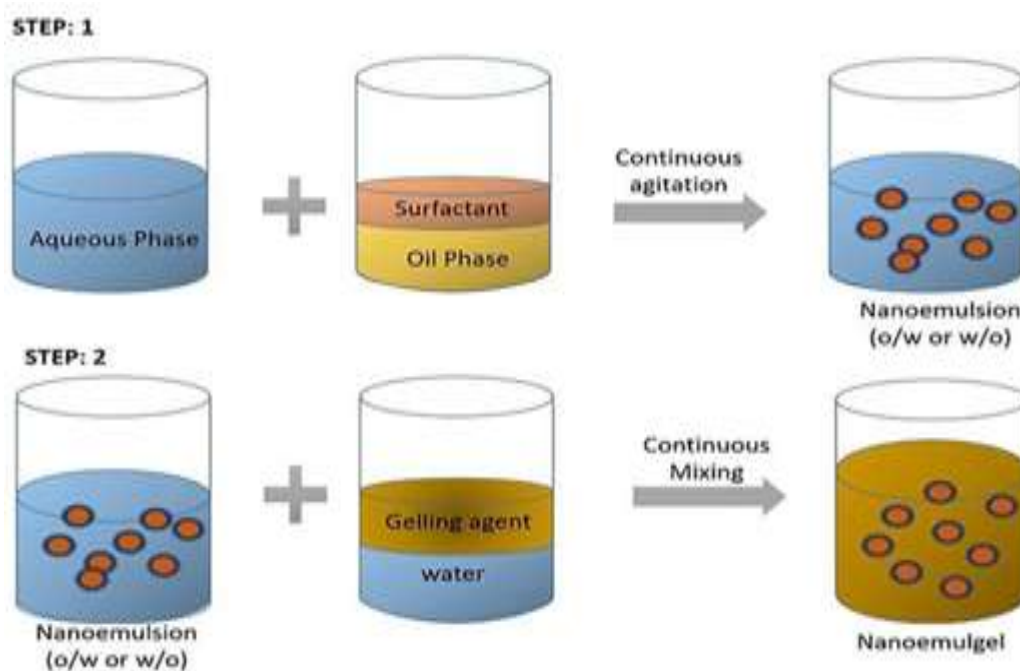


Figure 5. Represent the procedure for making a nanoemulgel

Methods used to make nanoemulsions can either be low-energy/high-energy emulsification techniques [49, 51]. In the high-energy techniques, mechanical energy is added to breakdown the oily droplet into tiny droplets that combine with the water. These techniques contain ultrasonication method and high-pressure homogenization method. Low-energy techniques, involves solvent displacement, phase inversion composition (PIC) methods, phase inversion temperature (PIT) methods, require less energy to

prepare nanoemulsions [21]. The selected surfactant either get combined with the oil/water part. Depending upon how well it get dissolves, the drug can be added to the water or oil part and dissolved. Then, one part get added slowly into the other with continuous stirring while maintaining the temperature that reaches the room temperature. An appropriate gelling agent mixed into water by constant stirring to make base of gel. pH should be adjusted, that prepared nanoemulsion incorporated into the base in a specific amount while keeping it stirred forms nanoemulgel.

Advantages:

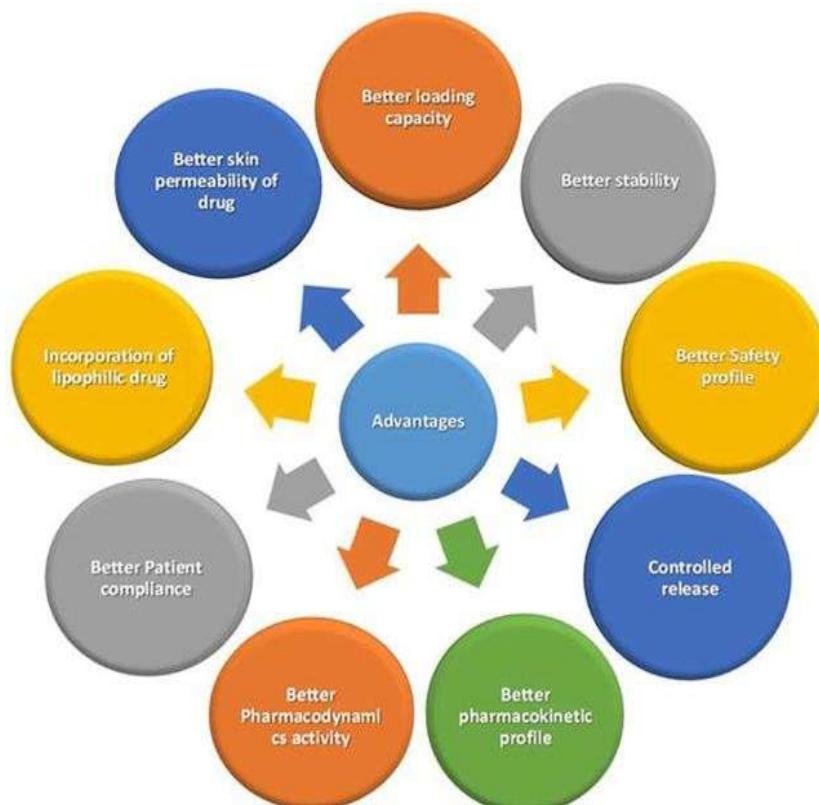


Figure6.Advantages

UsesofNanoemulgel:

Table3.UsesofNanoemulgel

TherapeuticArea	Uses
Antifungal	Clotrimazole,miconazoletotreatvaginalcandidiasis
Antibacterial	Metronidazole,clindamycintotreatbacterialvaginosis
Antiviral	Acyclovir,tenofovir totreatherpessimplexvirus(HSV)
Hormonal	Progesterone,estrogentotreatmenopause-related disorder
Immunomodulators	Enhancetheimmunedefense,preventingSTIs,treatingimmune-related disorders

IMMUNOLOGY OF VAGINAL MUCOSAL LAYER

IMMUNE SYSTEM OF VAGINAL MUCOSAL LAYER: It plays a critical role providing a defence against pathogens, while serving as a target for drug delivery. However, providing an essential site for local immune responses.

1. Proximity of Lymphoid Tissues:

- Mucosa-Associated Lymphoid Tissue (MALT) system contains part of vaginal layer, more specifically:
 - Contains Genital-associated lymphoid tissue (GALT)
- Having scattered B and T lymphocytes, macrophages, and dendritic cells
- Cervix (especially has a transformation zone) having many immune cells compared with vaginal walls.

2. Production of Cytokines:

These are those proteins that transmit signals which help to maintain immune responses, inflammation, healing. Vaginal mucosal layer contains:

- Pro-inflammatory cytokines:
 - IL-1 β , IL-6, IL-8, TNF- α
 - Initiated from infection, foreign substances
 - Promote new production of an immune cell
- Anti-inflammatory cytokines:
 - IL-10, TGF- β
 - Regulate, suppress an excessive immune effect
- Chemokines i.e. MIP-1 α , RANTES help recruit leukocytes into layers surfaces.

3. Activity of Immune Cell:

A variety of immune cells are active such as:

- Epithelial Cells:
 - Provides protection
 - Secrete mucins, defensins, cytokines
 - Possess pattern recognition receptors (PRRs), TLRs to indicate pathogens
- Dendritic Cell (DCs):
 - Help to capture an antigen, migrate towards lymph nodes
 - Present antigen to T cells that trigger adaptive responses
- Macrophages:
 - Phagocytose pathogens

- Produce the pro-inflammatory cytokines
- Langerhans Cell:
 - Specialized dendritic cells situated in the epithelial layer
- T Lymphocyte:
 - CD4+ T cell: Function as a helper cell, support the production of the antibody
 - CD8+ T cell: Function as a cytotoxic cell, kill infected cells
- B Lymphocytes, Plasma Cell:
 - Helps for the development of IgA, IgG

Challenges:

Since, vaginal layer has a unique immunological surrounding developed for maintaining security versus pathogens with potential tolerating non-harmful antigen (such as semen).

However, this balance creates challenges for achieving effective local immune responses, especially when delivering drugs or vaccines.

1. Rapid Clearance:

- Self-cleaning nature of the vagina leads to rapid clearance of drugs:
 - These secretions and mucus act as flushing out foreign materials.
 - Mild washing, menstrual flow, and gravity assist in rapid expulsion.
- This reduces adherence time of drug formulations, affecting absorption and local immune interaction.

2. Enzymatic Degradation:

- Vaginal mucus and epithelial secretions contain proteolytic enzymes such as:
 - Proteases, esterases, and nucleases
- These enzymes can:
 - Degrade peptides, proteins, and nucleic acids, making biologics (e.g., peptide drugs, DNA/RNA vaccines) particularly vulnerable.
 - Reduce antigen stability and bioavailability, limiting the generation of effective immune responses.

3. Variations of pH:

- The pH is normally acidic (around 3.5-4.5) because of development of lactic acid by Lactobacillus species.
- However, fluctuation is seen because of:

- Menstrual cycle
- Sexual activity (semen which is alkaline)
- Infections (e.g., in condition of bacterial vaginosis, the pH increases)
- Any change that affects pH can be:
 - pH-sensitive drugs or biologic that are inactivated
 - Impact enzyme activity
 - Damage immune balance, possibly increasing susceptibility for pathogens

Strategies involved for the Vaginal Immunity:

1. Use of Adjuvant:

These are those agents that advance the effectiveness of the immune effect. The vaginal immunology, they:

- Stimulated dendritic cell, Langerhans cell that support presentation of antigen.
- Trigger development of cytokine (e.g., IL-6, TNF- α , IFN- γ).
- Examples:
 - TLR agonists (e.g., CpG oligodeoxynucleotides).
 - Alum, saponins (QS-21) for mucosal application.

2. Pre-determined Release Systems:

These help for prolonging the residence for antigen/drugs at the vaginal cavity and enable

longer immune stimulation.

- Hydrogels, microspheres, nanoparticles are commonly used.
- Benefits:
 - Reduce enzymatic degradation.
 - Maintain stability over time.
 - Support a prime-boost response.

3. Targeted Systems:

It triggers uptake by mucosal layer that enhance presentation of antigen.

- Mucoadhesive polymers (e.g., chitosan, Carbopol) improve interaction with the vaginal mucosa.
- Nanocarriers like nanoemulsions, liposomes, and dendrimers can be engineered for:
 - pH-responsiveness
 - Temperature-sensitive release
 - Cellular targeting

NANOEMULGEL FORMULATION FOR IMMUNE ENHANCEMENT SELECTION OF ACTIVE PHARMACEUTICAL INGREDIENT (APIs):

A. Selection of APIs as Immunomodulators:

Increases, regulates the effect of immune system. Suitable to advance local immunity. Structures of API that can be used as shown in Figure 7.

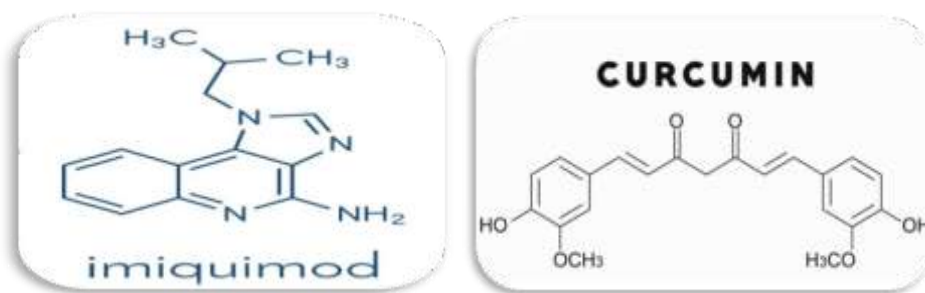


Figure 7. Structure of APIs as Immunomodulators Table 4. Immunomodulators

API	Role	Mechanism	Application
Imiquimod	TLR-7 agonist	Stimulates cytokine release (IFN- α)	Human Papilloma Virus (HPV)
Curcumin	Natural Immunomodulator	Macrophage modulation	Immune Enhancement
Chitosan (as adjuvant)	Mucoadhesive, immunostimulant	Enhances antigen uptake	To deliver the vaccine

B. Selection of APIs as Anti-inflammatory Agents:
 It controls the inflammation without slowing down the immune defence especially important at

mucosal applications. Structures of API of Anti-inflammatory agents as shown in Figure 8.

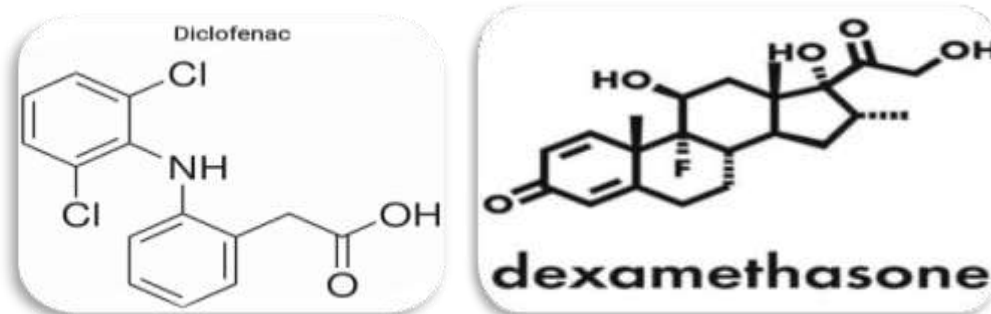


Figure 8. Structure of API of Anti-inflammatory agents Table 5. Anti-inflammatory agents

API	Class	Working	Application
Diclofenac Sodium	NSAID	COX inhibition	Effective in acute inflammatory states
Dexamethasone	Corticosteroid	Inhibit pro-inflammatory cytokines	Short-term use to avoid immune suppression

C. Antimicrobial Agents:
 Agents that kill the microbes while supporting immune balance, esp

pecially at sensitive regions like vaginal mucosal layer. Structures of API of Antimicrobial agents as shown in Figure 9.

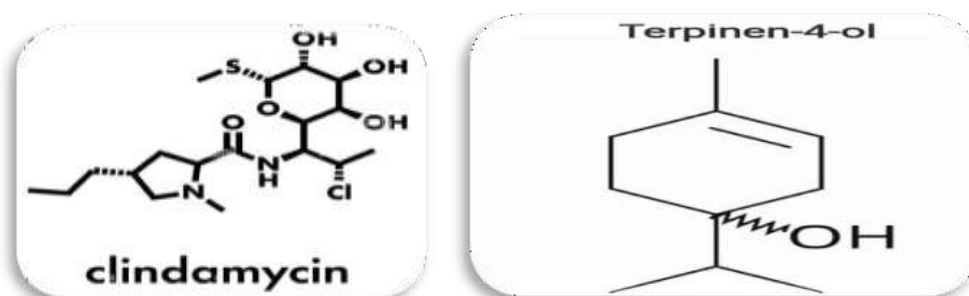


Figure 9. Structure of API of Antimicrobial agents

Table 6. API of Antimicrobial agents

API	Type	Target Microbes	Uses
Clindamycin	Antibiotic	Gram-positive bacteria	Used to treat bacterial vaginosis
Tea Tree Oil (Terpinen-4-ol)	Natural	Bacteria, Fungi	Used in low concentrations

FORMULATION DEVELOPMENT CONSIDERATION:

They are hybrid systems that combine properties of nanoemulsions as penetration-enhancing effect, good adherence and prolong release properties provided by gels. In immune enhancement, the goal is to deliver immunomodulators, antigens, or bioactives in a localized and sustained manner:

1. Compatibility of API with Excipients:

- Solubility & Partitioning:
 - API must dissolve in either aqueous/oil part of nanoemulsion.
 - Hydrophobic APIs (e.g., curcumin) go into oil part.
 - Lipophobic APIs may require co-solvents or surfactants.
- Poorly soluble drugs may crystallize or precipitate, affecting bioavailability.
- Chemical Compatibility:
 - Avoid interactions between API and excipients that can lead to degradation:
 - pH sensitivity
 - Hydrolysis or oxidation
 - Use antioxidants (e.g., tocopherol) or stabilizers if needed.
- Biological Compatibility:
 - Excipients must be non-irritating, non-toxic, and safe for mucosal or dermal application.
 - Common excipients include:
 - Oils: Isopropyl myristate, MCT, sesame oil.
 - Surfactants: Tween 80, Span 20.
 - Gelling agents: Carbopol 940, HPMC.

2. Stability Considerations:

- Physical Stability:
 - Avoid phase separation (creaming, coalescence) of the nanoemulsion.
 - Optimized droplet size and polydispersity index (PDI < 0.3).
 - Add stabilizers or increase surfactant concentration if needed.
- Chemical Stability:
 - Protect sensitive APIs from:
 - Light (use opaque containers)
 - Oxidation (add antioxidants)
 - Hydrolysis (maintain optimal pH)

- Microbial Stability:
 - Add preservatives like parabens, benzyl alcohol (ensure compatibility).
 - Conduct microbial load testing (especially for mucosal products).

3. Rheological Stability:

- Gel bases should maintain viscosity over time and temperature changes.
- Important for providing consistent application.

3. Release Profile:

- Controlled/Sustained Release:
 - Nano-sized droplets promote deep penetration into the layers.
 - Gel matrix triggers slow drug delivery, reducing dosing frequency.
- Rapid Burst Release Followed by Prolong Delivery:
 - Some immune-enhancing agents provide benefit by directly starting from burst release followed by prolonged delivery.
 - Done with adjusting concentration of gel using hybrid polymers.
- Release of Drug Modification Factors:
 - Viscosity of gel (higher = slower rate)
 - Crosslinking done by gel polymers
 - Oil-to-water concentration used in nanoemulsion
 - Type of surfactant, different concentration
- Evaluation to be Performed:
 - In vitro drug diffusion studies by using Franz diffusion cells apparatus.
 - Mathematical modeling: Korsmeyer-Peppas, etc.

NANOCARRIERS

ROLE FOR IMMUNE TARGETING:

1. Enhanced Cellular Uptake:

- Nanoscale Advantage:
 - Nanocarrier having (<400 nm) can penetrate epithelial barriers, reach immune cells like Langerhans cells, macrophages, dendritic cells.
 - Enhance the surface area and increase rapid drug release, bioavailability.

- Facilitated diffusion done by a process via Endocytosis:
- Nanocarriers are efficiently carried out by phagocytic and antigen-presenting cell (APCs) through:
 - Clathrin-mediated transport
 - Caveolae-mediated transport
 - Macropinocytosis
- Improved Intracellular Delivery:
- Enables delivery of immune-activating agents (e.g., cytokines, etc.) directly, increasing activation.

2. Immune Cells with Interactions:

- Antigen Presentation Enhancement:
 - Nanocarriers encapsulate surface-display immunomodulators.
 - Once internalized with dendritic cells, they convert MHC-I and MHC-II mediated antigen presentation, triggering an adaptive immunity.
- Modulation in Secretion of Cytokines:
 - Loaded nanocarriers can alter the modulation of cytokine profile, promoting either pro-inflammatory or anti-inflammatory cytokines as needed (e.g., IL-2, IFN- γ , IL-10).
- Targeting specifically Immune Cell Types:
 - Nanocarriers can be surface-modified by antibodies, ligands (e.g., mannose for macrophage targeting) to improve selective targeting.

3. Prolong, Localized Activation:

- Mucosal adhesive gel base have higher residence time, ensuring long-term interaction with mucosal cells.
- Prolonged release allows higher immune stimulation.

CASE STUDIES

CASE STUDY: ANTIFUNGAL NANOEMULSION FORMULATIONS:

Case Study 1 Example: Mentha spicata Oil-Loaded Nanoemulsion for Candidiasis:

Background: Candidiasis, especially vaginal candidiasis, is commonly caused by *Candida albicans*. Traditional antifungals often face resistance and side effects. Natural oils like Mentha spicata (spearmint) oil exhibit strong antifungal activity and can be used in nanoemulsion systems for improved efficacy.

Formulation Highlights:

- ✓ Oil part: Mentha spicata essential oil, which has antifungal properties
- ✓ Surfactant and helper surfactant: Tween 80 and PEG 400
- ✓ Aqueous phase: Water
- ✓ Gelling agent: Carbopol 934
- ✓ Process: First, combine water/oil together with high energy techniques making a stable mixture, then incorporate into gel base

Evaluation Parameter:

Measurement being checked to get better penetration, particle size that are about 100 nanometers. A proper amount of 30 mole is taken for proper zeta potential. Tests on real people show that penetration works better than oil or gel. Skin irritation tests show it's safe to use on the skin. Lab tests show it fights *Candida albicans* fungus. A rat model chosen, suffering with vaginal infection, helped reducing symptoms effectively.

Conclusion:

Nanoemulsion systems depict considerable signs for treating diseases like candidiasis, particularly those that employ natural agents like Mentha spicata oil. Particularly in cases that are resistant or recurrent, these formulations provide synergistic benefits in terms of efficacy, safety, and patient compliance.

CASE STUDY: IMMUNOMODULATORY NANOEMULSION SYSTEMS:

Incorporation of immunomodulatory agents like curcumin and polyphenol 60:

1. Curcumin-Loaded Nanoemulsion for Immune Enhancement:

Curcumin, a natural polyphenolic compound from *Curcuma longa*, exhibits effective immunomodulatory, anti-inflammatory properties. However, curcumin with low aqueous solubility, less bioavailability slows down the therapeutic potential. To overcome this barrier, a nanoemulsion system was developed:

- ✓ Formulation: Curcumin is delivered through a nanoemulsion containing oil part in water, which is then mixed into a gel base prepared from carbopol.
- ✓ Application: This product is applied on the surface of the skin, helps to manage long-term issues like psoriasis, dermatitis.
- ✓ Outcomes:

- It moves better through skin, stays there longer.
- It helps to control body's immune effect by lowering certain proteins (like IL-10 and TNF- α) that cause inflammation.
- It triggers steadily and causes less irritation when on application to the skin.

2. Polyphenol-60 Nanoemulgel to provide Local Immune Support:

It is a plant-derived antioxidant complex, commonly known as free radicals scavenging and immune-supportive effects.

- ✓ Formulation: Polyphenol-60 encapsulated in a nanoemulsion using natural oils (e.g., almond, sesame oil) and integrated into a thermosensitive gel base.
- ✓ Application: Vaginal/dermal route for immune protection, antioxidant defense.
- ✓ Outcomes:
 - Improved bioadhesion, residence time on mucosal surfaces.
 - Prolonged over 24 hours.
 - Enhanced macrophage activation, lymphocyte proliferation in vitro.

REGULATORY AND MARKET CONSIDERATIONS REGULATORY FRAMEWORK FOR VAGINAL FORMULATIONS:

In vaginal formulation, including creams, gels, hybrid systems like nanoemulgels, are considered specialized formulations that are regulated to ensure safety, efficacy, quality. Different regulatory bodies i.e. USFDA (USA), EMA (Europe), CDSCO (India) passed some guidelines for the approval, market authorization.

1) U.S. Food and Drug Administration (FDA):

- Regulatory Pathways:
 - NDA (New Drug Application) in support of novel chemical entities.
 - ANDA (Abbreviated New Drug Application) in support of generics.
- Relevant Guidelines:
 - Guidance for Industry:
 - Vaginal Microbicides – Developing Products to Prevent HIV Infection.
 - Scaling Up and Changes After Approval for Semisolid Products.
 - ICH Guidelines (Q1-Q10) for Safety, Quality, Effectiveness.
- Key Requirements:
 - In vitro drug release, permeation study.

- Localized tolerability, irritation testing.
- Reproductive, developmental toxicity study.
- Specific guidance in support of safety for excipient in vaginal application.

2) European Medicines Agency (EMA):

- Rule that controls the medicines that are meant to be used for humans is the Directive 2001/83/EC.
- Relevant Guidelines:
 - Rule that involves clinical testing of medicines, work locally on body.
 - ICH guidelines on safety, effectiveness, quality of medicines (ICH Q1 to Q12).
 - Key Requirements:
 - Vaginal pH compatibility.
 - Evaluation for local adverse effects.
 - Specific biocompatibility assessments.
 - Clinical trial tailored vaginal mucosal administration.

3) Central Drugs Standard Control Organization (CDSCO), India:

- Framework:
 - Drugs and Cosmetics Act, 1940 and Rules, 1945.
 - Relevant Guidelines:
 - Schedule Y – These are guidelines involved to do clinical trials, getting approval for new medicines.
 - BA, BE study guidelines.
 - Medical Devices, 2017 (these are having rules that apply if formulation used with a special device).
 - Key Requirements:
 - Need for permission from Drug Controller General of India (DCGI) to get allowance for new API.
 - Mandatory stability studies in tropical conditions (Zone IV).
 - Preclinical safety data specific to mucosal application.
 - Emphasis on local irritation, toxicity, and reproductive safety studies.

MARKETED TRENDS FOR VAGINAL FORMULATIONS:

Marketed vaginal formulation has faced significant extension because of more awareness on women's health, advancing the formulation technologies, and the demand for localized, non-invasive treatments. Market trends are shaped by both technological innovation and changing

consumer expectations.

1) Market Growth:

- Globally vaginal drug delivery market belong to increase at a CAGR of 6–8% over the next 5–7 years.
- Marketed drivers:
 - Rising incidence of bacterial vaginosis, vaginal infections, hormonal imbalances, and menopausal conditions.
 - Increasing demand for targeted delivery systems such as nanoemulsions, rings, films.
 - Expansion of OTC (Over-the-Counter), prescription-based women's healthcare products.
- Emerging economies, specifically in Asia-Pacific and Latin America, are showing rapid adoption due to improved healthcare access, awareness campaigns.

2) Preferences for Consumers:

- Non-invasive, self-administered products are preferred, especially for chronic or recurring vaginal conditions.
- Key consumer demands:
 - Ease of use (applicator-based gels, soft gels, pre-filled systems).
 - Lower side effects, reduced systemic exposure.
 - Fast onset of action, long retention time.
 - Natural or herbal-based ingredients, hormone-free options are increasingly favored.
- Rising interest in personalized vaginal health products, including pH-balancing, microbiome-friendly, and multi-functional formulations (e.g., antifungal + anti-inflammatory).

3) Innovation and Competition:

- New startups and biotech firms are joining the field with innovative solutions like mucoadhesive nanocarriers, temperature-sensitive gels, and smart delivery systems.
- Pharmaceutical companies are focusing on:
 - Managing the life of hormonal treatments by creating better vaginal versions of these medicines.
 - Changing existing drugs to be delivered directly to the vagina, which helps keep patents active longer.
- Partnerships between universities and companies are helping to create advanced products.

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