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A REVIEW ON BIOADHESIVE FILM FORMULATION FOR TREATMENT OF VAGINAL INFECTION

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ABSTRACT

Vaginal dose formulation is known for several drugs. The vaginal delivery system has many benefits, including a wide surface area and sufficient blood supply due to the lack of the first-pass metabolism. Novel methods of drug delivery have developed to lower the risk of vaginal infection. One such way is the 'Bioadhesive Vaginal Drug Delivery System' Film combines the advantage of gels and other pharmaceutical dosage forms. A vaginal film formulated with a plasticizer such as Glycerine, HPMC K4M, SCMC and, chitosan improves flexibility and overcomes mechanical tension. The Films prepared by Solvent Casting Method, unless it passes evaluation tests such as FTIR, DSC, Folding Endurance, *in-vitro* release in SVF (Stimulated Vaginal Fluid), *in-vivo* drug release profile. In comparison to other formulations, Vaginal Film is becoming more suitable and convenient. Self-insertion is possible because films are unlikely to be associated with leakage and messiness.

Keywords: Bioadhesive, Vaginal Film, Solvent Casting Method, Vaginal Infection, and Stimulated Vaginal Fluid

INTRODUCTION

1. Vagina:

The vagina usually refers to the vulva, including labia, vaginal opening, clitoris, and urethra as a female genital opening. The vagina, in addition to being a genital organ with function related to conception it serves as a potential route for drug administration **[1]**. It has the potential of delivering drugs for systemic effects and uterine targeting.

It has several roles within the female reproductive system:

1) Sexual intercourse – receives the penis and ejaculate and aids in their transportation to the uterus.
2) Childbirth – expands to provide a pathway for the delivery of a baby from the uterus.
3) Menstruation – serves as a conduit for the flow of menstrual fluid and tissue out of the body.

1.1 Histology of vagina:

Internal to external, the vagina is composed of four histological layers:

- Stratified squamous epithelium: This layer protects the cervical mucus and greases it (the vagina itself does not contain any glands) **[2]**.
- Lamina propria: It's a thick layer of connective tissue that protrudes through the epithelium and projects papillae. Here you'll find the more prominent veins.
- Fibromuscular layer: consisting of two smooth muscle layers: an inner circular layer and an outer longitudinal layer.
- Adventitia: A fibrous coating that gives the vagina extra strength while still tying it to the surrounding structures.

1.2 Pathophysiology:

The hydrogen peroxide produced by Lactobacillus acidophilus [normal vaginal flora] is toxic to pathogens and holds a stable vaginal pH between 3.8-4.2, respectively. Vaginitis occurs by pathogens announce into the vaginal flora and changes in the vaginal environment that enable pathogens to thrive **[3]**. Besides, candidiasis occurs by irregular growth of Candida albicans, which usually is caused by an imbalance in the atmosphere.

1.3 Vaginal secretions:

The vaginal discharge is a mixture of multiple secretions collected in the vagina from peritoneal, follicular tubal, uterine, Bartholin's, and Skene's glands **[4]**. Potent dosage formulations should preferably disperse in the vaginal canal immediately after injection in the presence of moisture to prevent inconvenience to users.

1.4 Enzyme activity:

The specific enzymatic activity of four different animals are sheep > guinea pig > rabbit ≥ human ≥ rat respectively.

The human genital tract has lesser enzymatic activity than the gastrointestinal tract, resulting in less protein degradation and peptide drugs in the vagina **[5]**.

1.5 Vaginal pH:

The healthy female genital tract's pH is acidic (pH 3.5–4.5) and is maintained within that range by bacterial alteration of glycogen from exfoliated epithelial cells to lactic acid **[6]**.

2. Vaginal infection:

In females, vaginal infection refers to inflammation of the vagina and vulva. Vaginitis considers by trichomoniasis-associated vaginal discharge, gonorrheoea, chlamydia, bacterial vaginitis, and yeast infection. The internal vaginal flora becomes unbalanced due to repeated vaginal infections, making it more difficult for sperm to enter the uterus **[7]**. Any condition that alters the vaginal acidity or disrupts the vaginal flora can increase the risk of infection.

2.1 Causes of vaginal infection:

- Hormones: Changes in your vaginal balance can occur during pregnancy, breastfeeding, or menopause (or if you're taking birth control pills) **[8]**.
- Diabetes: If your diabetes is uncontrolled, a rise in sugar in your vaginal mucus membranes (wet linings) will provide a breeding ground for yeast.
- Antibiotics: Many of the healthy bacteria that reside in your vaginal area can kill by these medications.
- Douches and vaginal sprays: The use of these products can cause your vaginal balance to shift.
- A low immune system: If you have HIV or another immune system disorder, the yeast can develop out of control as well.
- Sex: Although a yeast infection is not a sexually transmitted disease, it can be spread from one person to another through sexual contact.

2.2 Symptoms of vaginal infection:

- Burning, redness, and swelling of the vagina and the vulva (the outer part of the female genitals) **[9]**.
- Pain or burning when the patient pee
- Pain during sex
- A thick, white, odorless discharge, similar to cottage cheese

2.3 Classification of vaginal infection and severity:

One of the most severe and recurrent gynecologic complaints is vaginal infections.

They are as follows;

1) Vulvovaginal candidiasis: It occurs in yeast named *C. Albicans*. Vaginal edema or erythema was seen with a white curd-like appearance,

typically odorless, having ph less than 4.5

2) Trichomoniasis: It occurs in protozoa T. vaginitis. Dyspareunia, dysuria, and malodorous discharge observed. Vulvovaginal erythema occurs. Vaginal discharge is greenish-yellow, having ph 4.5 **[10]**.

3) Aerobic vaginitis: A greenish yellowish vaginal inflammation has a burning sensation in the introitus and vagina.

4) Bacterial vaginosis: The imbalance of vaginal flora causes bacterial vaginosis. In this, increased discharge, fishy odor, no dyspareunia occurs. Also, vaginal discharge is greyish, thin, homogeneous. Vaginal pH is higher than 4.5, and it has fewer signs of inflammation.

2.4 Treatment of vaginal infection:

Specific formulations like cream, gel, tablet, vaginal Film, vaginal ring suppositories are supported to treat common vaginal yeast infection. Estrogen creams or pills are for vaginal atrophy. Proper hygiene can help to avoid some conditions **[11]**. Wearing less breathable fabrics can also cause inflammation and discomfort in some women. Apart from this, adequate diagnosis helps ensure that the subject receives the proper treatment at the right time.

3. Vaginal drug delivery system:

There are specific marketed preparations available to treat vaginal infection. They are available in different dosage forms like cream, gel, ring, Film, suppository, injection, and tablet. Some of them are mentioned below in **Table 1**.

4. Vaginal Film:

4.1 Method of formulation:

The solvent casting process, solvent evaporation technique, Hot melt extrusion method, and Lyophilization method used to prepare vaginal films in general **[12]**. As shown in **Figure 1**, the process begins with preparing the film mass by dissolving or dispersing the drug and selected excipients in a suitable solvent. Once the film mass is ready and poured onto a flat surface, the mixture distributed, allowing the solvents to evaporate more quickly. The drying process may take place at room temperature or in ovens with direct heat or vacuum. The cutting phase will begin once the film mass has dried. Alternatively, the mixture poured directly into individual film molds—different dimensions and configurations of films designed to fit the desired therapeutic applications **[13]**. Finally, adequate packaging provides stability in storage conditions for future use and further investigation.

Table 1: Available marketed products for vaginal drug delivery system

Sr. No.	Antibiotics	Marketed Product	Company
1	Picasa	Oral suspension	Intas Pharma
2	Critposa	Injection	Cipla Pharma Pvt. Ltd.
3	Poshope	Injection	Abbott Pharma
4	Noxafil	Delayed-release tablet	Merk and Co. Inc
5	Posanat	Injection	Nacto Pharma
6	Noxafil	Oral suspension	Merk and Co. Inc

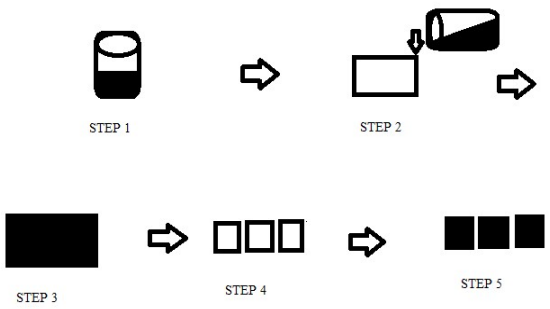

Figure 1: A diagram showing the general production process for vaginal films. Step 1: Preparation of film mass, Step 2: Pouring the mixture into molds, Step 3: Drying processes, Step 4: Cutting individual films, Step 5: Final packaging

4.2 Polymers/ Plasticizers used for film preparation:

4.2.1 HPMCK4M: The matrix-forming ingredient must have good mechanical strength and sufficient peel strength. Even so, HPMC films made with organic solvents, such as a mixture of methanol and dichloromethane, are commonly used in film formulation **[14]**. The cellulose derivatives' molecular weight is significant; the lower the molecular weight, the lower the viscosity and film-forming capacity.

4.2.2 Sodium CMC: It is used along with HPMC. It plays a role in film formulation with a specific concentration ratio of the polymer (HPMC) and copolymer (sod. CMC) cast superficially. It imparts viscosity as it is cast-off as a thickening agent, emulsifier, chelating agent, thereby, in addition to this, sod. CMC has an excellent film-forming ability, is biodegradable, and has low toxicity **[15]**. Moreover, it improves the performance of composite films and has a stable internal network structure.

4.2.3 Plasticizers: Plasticizers are essential in film formulation because they provide justice and protect the Film from environmental stress. It should be flexible, easily folded for insertion, and have a good affinity with the adhesive. Typically, plasticizer for film fabrication is small organic molecules with high boiling point. Examples of such plasticizers include; glycerine, polyethylene glycol 400, Lactic acid, Tartaric acid, Oleic acid, and propylene glycol; add plasticity to film formulation **[16]**.

4.3 Evaluation tests:

4.3.1 Characterization studies:

a. HPLC analysis: this study analyzes the data and separates the analyte to know the components' purity **[17]**.

b. FTIR studies: In this study, the compatibility, i.e., The Fourier Transform Infrared Spectroscopy (FTIR) instrument, can detect any chemical reaction between the polymer and the drug.

c. X-Ray Diffraction (XRD): This study aims to assess the physical form (Crystalline or Amorphous) of pure drug, polymer, blank film formulation, and drug-loaded film formulation of pure drug, polymer, blank film formulation, and drug-loaded film formulation.

4.3.2 Post formulation studies:

a. Film weight and thickness: The appropriate weight and thickness of Film are determined using a micrometer.
b. Folding Endurance: The film formulation should be folded repeatedly in one place until breaks show the film formulation's flexibility. It should withstand a minimum of 200 folds.
c. Mechanical Properties: In this study, the mechanical hardness and *in-vitro* adhesion of film formulation are deliberate using a texture analyzer operated by Texture Exponent 32 software. It determines the tensile property of the Film.
d. Film pH and Adhesive Property: the pH of the Film must be compatible with the vaginal film pH, i.e., 3.8 to 4.5, and adhesive property with drug release is determined in stimulated vaginal fluid [SVF] carried out in Franz diffusion cell **[18]**,**[19]**.
e. Swelling and Morphological Study: It determines the morphological characteristics of drugs and excipients along with their swelling index.
f. Characterization of hydrophilicity/hydrophobicity: The behaviour of Film at the administered site. By using Franz diffusion cell, the quantity of drug released per unit time is check.
g. *In-vitro* cell studies: This test works to test the Film's cytotoxicity on the genital tract cell. Standard cell lines such as; HeLa cervical, CasKi cervical, HEC-1-A endometrial, or VK2/E6E7 vaginal epithelial cells play a role in vaginal formulation **[20]**.
h. *In vivo* studies: Female mice, rabbits, and macaques are used

in in vivo experiments to test vaginal films. When inserted in the vagina, the Film should be comfortable for the animal. However, care supports avoiding an explosion of vaginal Film due to natural body movements.

4.4 Sustain and control drug delivery system:

The aim of excipient selection and combination during formulation is to help create an optimal dosage form, enhance the dosage form's therapeutic activity and stability, and ultimately minimize drug-related toxicity by providing sustained-release or control release, depending on the formulation **[21]**. Films are a type of controlled-release dosage form that keeps the drug in your system for a long time after you inject it **[22]**.

5. IDEAL CHARACTERIZATION OF INTRAVAGINAL DRUG DELIVERY SYSTEM:

- By removing the microbicide in a regulated manner over a long time, it provides immediate and long-term security **[23]**.
- Have adequate retention and distribution in the vaginal area
- Be able to fight a variety of pathogens, including STIs and HIV
- Simple to manufacture, cost-effective, and easy to apply, thus facilitating patient compliance
- It is non-irritating and does not cause any physical pain
- A part can melt at 36 °C, which is vaginal temperature
- Intravaginal drug delivery devices should be non-toxic
- There should be no meta-stable forms
- The preparation should have wetting and emulsifying properties.
- It should have the required viscosity to prevent leakage from the vaginal region (in the semisolid dosage form) **[24]**.
- Increase the contact time between the membrane and the prepared Film because the preparation should have proper sticking properties.

6. FACTORS AFFECTING INTRAVAGINAL DRUG DELIVERY SYSTEM:

- Poor personal hygiene
- Obesity
- Stress
- Sexual partners have changed
- Pregnancy, recent childbirth, or menopause
- Antibiotics and oral contraception are overused

- Having unprotected sex with someone who has an STD
- Menstruating teenagers
- Inadequate sleep
- Deodorants, douches, and scented sanitary products are all used by women **[25]**.

7. ADVANTAGES:

- Ease of access and high blood supply
- The reduced side effect with great permeation area
- High vascularization and low enzymatic activity
- Avoidance of the first-pass metabolism
- Self-administration is possible **[26]**,**[27]**.

8. DISADVANTAGES:

- Gender specificity
- Genital hygiene issues
- Menstrual cycle associated with vaginal changes
- Coitus interference
- Local side effects
- Variable drug permeability
- Pain, redness, vaginal irritation
- Tenderness at the targeted site
- Frequency of doses 2 to 3 times a day
- Chances of overdoses
- Repeat application is inconvenient.

9. APPLICATIONS OF INTRA VAGINAL DRUG DELIVERY SYSTEM:

- For vaginal immunization, this route of drug administration is beneficial
- Using vaginal contraceptive films on a multi-cycle basis
- Treatment for the vaginal infection that is successful throughout
- A simple method for treating a fungal infection in the local area
- Hormones can be delivered using this method.

10. CONCLUSION:

This review explains the development and stages of film formulation along with an example of some marketed preparations used to treat vaginal infection. Along with Vaginal infection, this review hypothesizes the film formulation's safe outcomes, suggests a standard method to prepare it. Furthermore, this review indicates the importance of film formulation and selection of polymers and plasticizers. Additionally, it includes evaluation parameters before developing the film formulation and tests after preparing the formulation.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

'Dr. Rupalben Kaushalkumar Jani' designed the study, wrote the protocol, 'Shrestha Dayanand Ubana' wrote the first draft of the manuscript, and 'Goswami Kaushal Puri' managed the literature searches. All authors read and approved the final manuscript.

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