



VAGINITIS: RECENT FORMULATION APPROACHES OF ANTI-INFECTIOUS DRUGS

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ABSTRACT

Vaginitis is mostly caused by *Trichomonas vaginalis* leading to mild to severe infections in the vaginal mucosa. The treatment for this disease can be initiated with the help of antimicrobial and antifungal agents in various dosage forms. Novel dosage forms have gained prior significance in recent formulation researches due to their inevitable controlled drug release mechanism and site specific applications. These systems include nanoparticles, micro particles, hydrogel systems, mucoadhesive systems, *In-situ* gels, etc. The physicochemical and biopharmaceutical parameters of the drug greatly influence the selection of the dosage form design. The attempt of this review is to enlighten the various novel approaches adopted for the design of antimicrobial and antifungal agents, such as Secnidazole, Fluconazole, Metronidazole, etc., with special emphasis on the treatment of vaginitis. Development of novel dosage forms of these antimicrobial agents would be a suitable way to achieve better therapeutic result against vaginitis.

KEY WORDS: Vaginitis, Antimicrobial, Antifungal, Novel dosage forms, Biopharmaceutical



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INTRODUCTION

Vagina serves to be a potential site for delivering drugs in addition to be a genital organ in females. Normal vaginal flora are prone to various disorders and diseases due to changes in normal physiological condition or due to induced external stimuli. The most common vaginal infection is vaginitis, which includes inflammation of the vagina. It is stated that the incidence of vaginal infection is due to Trichomonas, Bacterial vaginosis and candidiasis^{1, 2}. It results in unusual discharge among pregnant women, resulting in pruritus and discomfort in the region of the vulva. It may sometimes affect birth rates in such women³. Since vaginal morphology is highly dynamic with respect to absorption of drugs, their metabolism and elimination these conditions can generally be treated with the help of conventional formulations that delivers steroids, antiprotozoal drugs, antiviral drugs, antimicrobial drugs and antifungal drug. Though the conventional formulation aids to control vaginal infections, it poses various disadvantages to patients, such as discomfort during the application of the medicaments and low residence time, so there is a need to develop novel approaches in producing therapeutic products.

Bacterial Vaginosis

The microbiota of a normal healthy vagina comprises of certain bacteria which forms a critical defense layer against harmful pathogen, it comprises of bacteria namely *Lactobacillus* mainly in the lower genital tract⁴. The bacterial vaginosis (BV) occurs most commonly among pregnant women and women who are sexually active. Bacterial vaginosis is the condition wherein the normal *Lactobacillus* species are replaced with harmful anaerobic microorganisms such as *Gardnerella vaginalis* and *Bacteroides* species. The incidence of Bacterial vaginosis makes the female vagina highly prone to infection such as HIV and other sexually transmitted diseases⁵. The most symptoms and signs can be commonly diagnosed by the vaginal discharge which is

highly homogenous and appears to be white gray with an unpleasant odor (especially after sexual intercourse), though the gray discharge coats the walls of the vagina, it does not lead to any kind of irritation. Itching, soreness and redness around the vulva and vagina is more common and vagina becomes more alkaline in pH^{6, 7}.

Vaginal Trichomoniasis

Trichomoniasis is caused by protozoan namely *Trichomonas vaginalis* which leads to vaginitis in female and it is considered to be the most common cause of sexually transmitted infection. In male Trichomonas are detected in prostatic tissue in benign prostatic hyperplasia, prostatitis and in men having prostate cancer. Trichomoniasis may also increase the transmission of human immunodeficiency virus (HIV) by two- to three folds both in male and female^{8, 9}. Trichomonas infects both male and female, however, only female shows symptoms male remains asymptomatic. Growth of Trichomonas on vaginal membrane could result in vaginal discharge that smells fishy and appears to be frothy and yellow colored. The severity of this condition is observed when blood starts to ooze out from the vagina and post coital¹⁰.

Vaginal Candidiasis

Vaginal candidiasis is caused by Candida microorganisms and it is responsible for causing the yeast vaginitis. Of all the species of Candida, *Candida albicans* tends to cause major vaginal disorders. *Candida glabrata* is another species that could be a cause of vaginal disorders. The disease condition can be treated either with topical azoles or systemic azole (fluconazole or ketoconazole). The major problem in treating patients with Candida vaginitis is that this organism develops resistance to topical and systemic azoles¹¹.

Diagnosis of Vaginitis

Generally, patients affected by vaginitis can be diagnosed by Amsel's criterion⁶ which is highly significant. According to Amsel's criteria, the vaginal discharge is homogenous (color and amount varied from normal discharge). Addition of potassium hydroxide to vaginal secretion produces an amine odor (WHIFF TEST). Microscopic examination of vaginal fluid reveals clue cells. Generally there is a notable change in pH of vagina higher than 4.5.

Conventional Formulations

The majority of commercially available vaginal delivery systems are usually targeting topical administration. Conventional formulations available for various drugs to treat vaginal disorder are given in the table. Vaginal tablets may contain binders, disintegrants and other excipients that are used to prepare conventional oral tablets. Formulating very hydrophobic drugs as vaginal tablets may not

be an ideal approach moreover; attempts have been carried out to use mucoadhesive polymers in vaginal tablet formulations in order to increase the residence time^{12, 13}. Creams and gels are another type of delivery systems frequently used. Creams are normally emulsions whereas gels are usually hydrophilic polymers that utilize covalent bonds to create cross-linked three-dimensional¹⁴. However, a disadvantage that can be associated with the use of creams and gels is that they may not provide an exact dose, thus compromising the efficacy of the drug therapy. Ideally, a vaginal drug delivery system that is designed for local effect should distribute uniformly throughout the site of action. However, the distribution and coverage of formulation within the vaginal cavity varies with the properties of the delivery system. It was reported that disintegrating tablet show low coverage whereas solution, suspension and emulsions display greater distribution profile¹⁵.

Table 1
List of drugs and their dosage forms available to treat vaginal infections.

Class	Drugs & Reference	Formulations
Azalide	Azithromycin ¹⁷	Tablet
Triazole	Fluconazole ¹⁶	Tablet
Imidazole	Secnidazole ¹⁷	Tablet
	Miconazole ¹⁶	Gel, cream, ovule
	Metronidazole ¹⁶	Tablet, suspension, injection
Antifungal	Nystatin ¹⁸	Cream, ointment, oral tablet, suspensions, vaginal tablets
	Clotrimazole ¹⁶	Spray, tablet, cream, suppository
	Natamycin ¹⁷	Tablet
lincosamide antibiotic	Clindamycin ¹⁸	Cream, suppository
Antiseptic	Povidone iodine ¹⁶	Solution, spray, ointment,

Novel Formulations

A novel formulation of antimicrobial or antifungal drugs could be a solution to overcome the limitations of conventional formulations such as tablets, cream, gel or ointment. The major disadvantages with such formulations include their less effectiveness to deliver drugs in a controlled manner and poor bio adhesive nature¹⁹. The treatment could be highly enhanced and can be made more

patient compliance by developing a novel formulation.

Vaginal Suppositories

Suppositories are intended to bring about local action in the treatment of vaginal disorders. These are generally conical, rod or wedge shaped and can be inserted into vagina. Generally suppositories are prepared by the fusion method using various bases and polymers that melts or softens at body

temperature. Molds made of metal or plastics are used in the preparation of vaginal suppositories²⁰. In a clinical phase 3 study conducted by Fabia *et al.*, (2007) the tolerance level and efficiency of a vaginal pessary that comprising of Miconazole (200 mg) and Metronidazole (750mg) in 92 women patients affected by vaginitis were studied. In this study, the patients were advised to insert the vaginal pessary containing 750 mg of Metronidazole and 200 mg of Miconazole nitrate for seven nights. Swabs and spatula were used to collect vaginal samples for evaluation. They could clinically diagnose the type of organism responsible for causing vaginitis in each patient during the course of their study. The most prevalent form of vaginitis was fungal vaginitis in 27 patients, 16 patients were affected by bacterial vaginitis and 1 woman was found to be affected by *Trichomonas vaginalis*. The addition of 10% potassium hydroxide revealed the presence of spores or hyphae on wet smears confirming the identification of Vulvovaginal candidiasis. 0.9% physiological saline solution was used to detect *T.vaginalis* by identifying the mobile protozoan on vaginal wet smear. By treating the patients with the pessary of Metronidazole and Miconazole for seven day regime, the patients showed remarkable changes in disease state and symptoms. This was evident from the vaginal discharge of all the patients after the treatment which was found to have fewer odors and the color of the discharge was less gray². Zawar L.R and Bhandari G.S (2012) have prepared sustained release suppositories of Ondansteron using polaxamer as a base. They have made use of swellable polymers HPMCK4M and Methocel. The prepared formulation showed sustained release of Ondansteron for 12 hours. Increase in polymer concentration prolonged the release of drug from the formulation. A formulation containing drug polymer in the ratio of 1:3 showed release up to 97.47% at the end of 9h. Thus the polymer concentration influenced the release of drug from the formulations. They have evaluated the formulations for various parameters such as hardness, melting point,

disintegration time and weight uniformity and liquefaction time²¹.

Bilayer Pessaries

Multifunctional bilayer pessary was prepared by Vinital kale *et al.*, (2012) containing probiotic and prebiotics in separate layers. This helped in releasing probiotic at first so as to create favorable condition for growth of probiotic in vaginal mucus. This bilayer pessary helped in maintaining the normal microbial flora which prevents the growth of harmful microbes to a great extent. Lyophilised *lactobacillus* species were used as probiotics in the pessary. The prepared formulation was evaluated for uniformity of weight, mechanical strength. The survival of probiotics in the formulation was studied using the plate count method. The bilayer pessary was a suitable alternative for delivering chemically incompatible drugs with varying release and activity²².

Vaginal Tampon

Medicated vaginal tampons are solid; single-dose preparations intended to contain the mass of absorbent material that are generally used to be inserted into the vaginal cavity to absorb vaginal discharge²³. Kunihiro *et al.*, (2012) proposed a novel treatment regimen in their clinical phase study among 64 women aged between 18-37 years. They have made use of vaginal tampon containing 10% solution of activated charcoal and control group containing 100 mg chloramphenicol vaginal suppository. The proposed treatment maintained the level of *lactobacillus* species in vaginal flora to preserve a healthy microbial ecosystem rather involving in eliminating harmful microbial growth. By means of activated charcoal there was only less loss of *lactobacillus* when compared with chloramphenicol, which showed complete loss of *lactobacillus* in vaginal microflora. Also, there was significant reduction of vaginal pH. This novel method explained the use of non antibiotics as an alternative therapy, as transvaginal supplement of *lactobacillus* species⁶.

In-situ Gel

A system that forms gels from sol state at the site of action is termed as *in-situ* gel. This change in phase is due to various physico chemical aspects such as temperature, pH and ion mediated²⁴. Lokhande *et al.*, (2004) have developed pH triggered In situ gelling system of ciprofloxacin. They used carbopol934 and HPMC for the preparation of pH triggered *in-situ* gelling system that delivered the drug in sustained manner²⁵. Narayana *et al.*, (2009) have prepared ion triggered *in-situ* gel using gellan gum as polymer along with sodium carboxy methyl cellulose for local release of Secnidazole for treating vaginitis caused by *Trichomonas vaginalis*. The prepared *in-situ* gel was evaluated for various parameters such as pH, mucoadhesive force, viscosity, gel strength, gelling capacity, spreadability, drug release kinetics. The prepared formulation showed increased rate of residence and improved therapeutic effects. The *in-situ* gel had better patient compliance since the formulation could be applied in the form of solution followed by conversion into a gel at the site²⁶.

Effervescent Bio Adhesive Vaginal Tablets

Patel *et al.*, (2010) have prepared effervescent bio adhesive vaginal tablets of Ketoconazole against *C. albicans* infections by the direct compression method using methyl cellulose and carbopol 941 as bio adhesive polymers. The investigation of antifungal activity of the prepared tablets was compared with previously marketed products candid V3 and candid V gel. Mucosal membrane of rat, pig, bovine and cow were used to study the mucoadhesive strength of tablets. The tablets were examined for proper swelling since it was important for adhesion of tablets to the vaginal mucosa. The type of polymer used and polymer concentration controlled the mucoadhesive property of the tablets²⁷.

Bio adhesive Films

Bio adhesive films are generally made of polymers through solvent evaporation method. Since polymers adhere to the vaginal mucosa to greater extent bio adhesive film enhances

bio adhesive property and overcomes the problems such as leakage and uneasiness caused by conventional formulation such as tablets, suspension, creams²⁸. The major advantages of using bio adhesive films are easy to store, easy to apply, Aesthetic appeal and it maintains stability of the drug.

Ovules in Treatment of Vaginal Disorders

The ovule is a medical device that could supply desired dosage form vaginally to treat vaginitis and it is similar to vaginal suppositories. It is stated that the topical use of Metronidazole gained its importance from standard usage of oral Metronidazole since 1978. Comparison of Metronidazole gel with the ovules of Metronidazole and Nystatin was done by Sixto Sanchez *et al.*, (2004). It was evident from their clinical trial that the occurrence of Bacterial vaginosis was lesser after treatment with Metronidazole plus Nystatin ovules than after treatment with gel of Metronidazole²⁹. Thus, this clinical study conducted at Dos de Mayo Hospital in Lima, Peru provoked the use of vaginal devices such as ovules that could bring better therapeutic results.

Micro particulate Systems in Vaginal Delivery

Micro particle system generates sustained release of drug providing effective release of antifungal drugs. Furthermore a micro particle system possesses an enhanced stability. M.J. Martín-Villena *et al.*, (2013) have prepared the formulation of the Nystatin loaded micro particles. They have prepared three types of micro particles namely poloxamer 407 coated alginate, alginate micro particles and chitosan and to test the efficacy they have carried out DSC and FT-IR studies. The characterization study revealed that the micro particles were spherical in shape and mean particle sizes ranged from 36.088 μm to 56.146 μm . The alginate and chitosan coated micro particles showed similar encapsulation efficiency and it was lower for poloxamer 407 coated micro particles³⁰.

CONCLUSION

Vaginal route proves to be a promising way for controlled delivery of various drugs through novel formulation. The current review deals with some of the novel dosage forms of various antimicrobial and antiviral agents. The disadvantages faced by using conventional dosage forms can be easily overcome by the novel dosage forms. It has been a most preferred research area to overcome various

vaginal disorders including STD's and to prevent the transmission of HIV to a great extent.

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