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# REVIEW ON VAGINAL DRUG DELIVERY SYSTEM

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**ABSTRACT**

Many efforts have been made for drug administration through alternative routes after the poor absorption of drugs through oral route. Then the vaginal drug delivery system has been rediscovered for drug absorption. This system has been known and followed from the ancient times. This is the best route and has the potential for the administration of proteins, peptides and many other therapeutic drugs like macro-molecules. For the administration of drug like contraceptives, steroids, metronidazole and anti-retroviral, vaginal drug delivery is the most optimal and favorable route. Hepatic - gastrointestinal first-pass metabolism, gastric impatience of drugs and vacillation of dosing interval possibilities can be prevented by the continuous infusion of drugs through vaginal mucosa. The rate and effect of drug absorption through vaginal route depends on the physiology of vagina, stages of menstrual cycle, age, pathological conditions, health conditions and formulation factors. Various dosage forms like suppositories, gels, creams, ointments, foams, vaginal rings are used in vaginal drug delivery system. The benefits of vaginal drug delivery system are it increases the bioavailability, least systemic side effects; easiness of use and self-medication is possible. However vaginal drug delivery system is considered as a less effective route because of the unfortunate absorption of drugs across the vaginal epithelium. This review gives an explanation of vaginal physiology, drug absorption through vagina, advantages and disadvantages and many other features of vaginal drug delivery systems and its pharmaceutical aspects.

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## INTRODUCTION

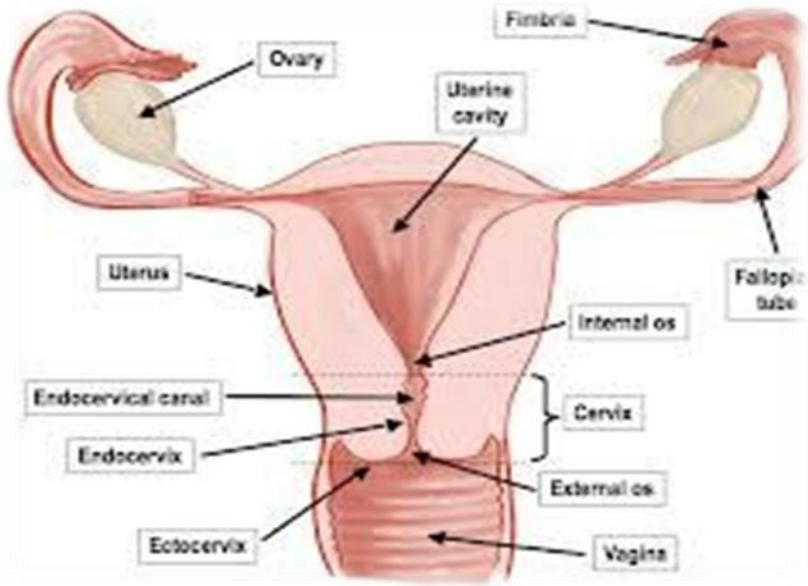
Vaginal route is the vital route for the drug administration due to the avoidance of first pass effect, vascularization, permeation area and low enzymatic activity [1]. Many researchers have been concentrating on the vaginal drug delivery system for the alternatives of oral and parenteral drug administrations. This vaginal route is mainly used for administration of various drugs like contraceptives, suppositories, anti-fungal and anti-microbial agents. This route possesses many advantages of reduction of gastrointestinal and hepatic side effects and targeting of drugs to reproductive organs. The formulations and agents which are administered vaginally are mainly developed to provide a therapeutic effect known as "Dual Prophylaxis" for the protection and prevention of some microbial infections which include AIDS and STD's. Several drug delivery technologies are used for vaginal drug administration. The presence of a thick and dense network of blood vessels made vagina the best route for both the systemic and local effects. Vagina has a great potential for delivering wide range of systemic compounds like proteins and peptides [3]. Most commonly used vaginal drug delivery systems are creams, tablets, foams, gels, ointments, suppositories and tampons. The vaginal dosage forms which are available have some limitations such as disorderliness, leakage, low residence of time and loss of therapeutic efficiency. Researches and studies are being done on vaginal drug delivery systems to accomplish the requirements.

## ANATOMY AND PHYSIOLOGY OF VAGINA

Vagina is a muscular tube which lengths about 6-10cms long approximately extending from the cervix of the uterus. Vaginal wall is comprised of three layers

- Outer Adventitial Layer
- Middle Muscularis Layer
- Inner Mucosal Layer

The presence of vaginal folds and micro-elevations on the epithelial cell surface permits the vagina to expand and allow the placement of vaginal formulation and increases the surface area of vagina and improves the drug absorption. The vagina has many features in vaginal secretions like pH, enzyme activity and micro-flora [7]. These factors affect the formulation spreading, retention, absorption and drug discharge in vagina. The vaginal epithelial layer changes by 200-300Am during menstrual cycle. The existence of smooth elastic fibers in the muscular coat helps in vaginal elasticity. This elasticity is further increased by the loose connective tissue of tunica advent. Internal iliac artery, uterus, middle rectal and internal prudential artery are the blood vessels which stream blood to the vagina.




***Structure of female reproductive system.***

Desquamated vaginal cells and leucocytes along with cervical secretion and transudation from blood vessels constitute vaginal fluid. Endometrium and fallopian tube secretions also contribute for vaginal fluid. The amount and composition of vaginal fluid change throughout menstrual cycle. The pH of vaginal fluid is maintained between 3.8 and 4.2 by lactobacillus acidophilus produced by lactic acid which acts as a buffer in the vagina [11]. The pH of vaginal fluid may increase during menstrual period because both the ejaculate and vaginal transudate are alkaline in nature. The pH also changes with respect to age, health conditions, and stage in menstrual cycle, estrogen levels, levels of cervical mucus and infections. The enzymatic activity of human genital tract is less when compared to gastrointestinal tract for less degradation of proteins and peptide drugs in vagina.

**VAGINAL ROUTE OF DRUG ABSORPTION**

Drugs are transported into the vagina by two methods namely intra-vaginal and trans-vaginal through the vaginal mucosa of the uterus and systemic circulation.

Absorption of drugs through vaginal route occurs in two steps;
- Drug dissolution in lumen
- Membrane Penetration

Most commonly used drugs in vaginal route are contraceptive steroid hormones. Many physiological and physicochemical properties affect the drug absorption across the vaginal epithelium. Vaginal yeast infections are treated by antifungal agents like tioconazole, clotrimazole and miconazole which are orally administered. Based on the anatomical and physiological features of vagina others drugs are further formulated for drug delivery in future.

**FACTORS AFFECTING DRUG ABSORPTION**

The transport of drug through the vaginal membrane tales place in three major distinct ways namely:
- Transcellularly
- Paracellularly
- Vesicular or Receptor Mediated Transport

The amount of drug concentration after intra-vaginal administration depends on the following factors
- Physiological Factors
- Physicochemical Factors

**Physiological Factors**
- Rate of change in epithelial layer thickness
- Cyclic Changes
- Change in hormonal level
- Vaginal fluid volume
- Vaginal pH alteration
- Sexual Arousal

**E.g.**

Absorption of steroids is affected through vaginal route by the thickness of vaginal epithelium.

**Physicochemical Factors**
- Liphophilicity
- Ionization
- Molecular Weight
- Surface Area
- Chemical Nature

**Advantages of vaginal drug delivery system**
- Prolonged Release
- Low Systemic Side Effects
- Increase in Bio-availability
- Effective for orally inactive drugs
- High vascularization
- Low enzymatic activity
- Avoids First-Pass Metabolism
- Self-Medication is possible
- Compared to oral dose less dose is used
- Interaction with digestive juice is avoided and drug degradation is minimized
- Quick onset of action

**Dis-Advantages**

- Gender Specificity
- Patient Incompliance
- Local irritation of drugs
- Few drugs can only be administered
- Change in drug absorption related to menstrual cycle, menopause and pregnancy
- Sexual Intercourse
- Personal Hygiene
- Drugs sensitivity at vaginal pH

**VAGINAL DOSAGE FORMS [13]**

Several considerations should be followed in the advancement of vaginal dosage forms.

- Optimal pH maintenance for vaginal epithelium
- Easiness of application
- Uniform dispersal of drug
- Retaining time in vagina
- Compatibility with co-administered drugs

There are many other forms of drugs or formulations which are applied vaginally.

- Vaginal Tablets and Suppositories [18]
- Vaginal Foams, gels, creams and [17]
- Vaginal Rings [20]

**Vaginal Tablets and Suppositories**

Numerous dosage forms or large number of intra-vaginal delivery systems are available in form of tablets and suppositories. These are the formulations which are designed to dissolve in the vaginal cavity and discharge the active components over an extended period of time. These suppositories are mainly intended for localized effects primarily as contraceptives, antiseptics and anti-fungal. Drugs administered as suppositories include dehydroepiandrosterone sulfate for maturation effect on the uterine cervix, miconazole for vaginal candiasis and progesterone for hormonal replacement therapy. Binders, disintegrant and additional excipients are obtainable in vaginal tablets which are used to formulate predictable oral tablets. They have the advantage use of ease of production and insertion. Vaginal residence time is increased by using mucoadhesive polymers in vaginal tablet formulations. Itraconazole, clotrimazole and prostaglandins are some drugs that are directed as vaginal tablets. Absorption of drug from a vaginal formulation is decreased by the presence of aqua-phobic and release impeding materials. Highly aqua-phobic drugs might not be appropriate for vaginal tablets. Polystyrene sulfonate (PSS) is developed in the form of vaginal tablet as it shows highly or superior anti-microbial activity in contradiction of HIV and HSV. Presence of diffusion enhancers like surfactants and bile salts can considerably enrich the absorption of drugs in vagina.

**Vaginal Foams, Gels and Creams**

Creams, gels and foams are used for current distribution of contraceptives and anti-bacterial drugs. These dosage forms are very difficult and hard to apply and uncomfortable when they leak or spread into the undergarments and cloths. Due to non-uniform distribution and leakage creams and gels might not deliver an exact dose. Desired properties of gels and creams are conventional and viable in vaginal administrations. The gels, foams and creams used in vaginal formulations should be tranquil to use, non-toxic and non-irritating to the mucous membrane. Metronidazole and Clindamycin vaginal cream are found to be effective as orally administered drugs in treatment of bacterial vaginosis. Vaginal creams and gels are based on the principle of liquid emulsion or hydrogel based drug delivery. When these hydrogels are sited in aqueous environs or medium they swell and hold huge volumes of water in their enlarged structure and release drug in a restrained manner. Vaginal gels have also been used for intra-vaginal vaccine delivery. Cervical maturation, induction of labor and antibacterial agents are also accessible in the form of vaginal gels. Most usually used drugs for cervical maturation and labor induction are oxytocin, dinoprostone and misoprostol. Vigorous microbicidal activity is possessed against HIV, HSV, Chlamydia trachomatis and Neisseria gonorrhea, by minocaprin hydrogel formulation which is less cycotic than nonoxynol-935. Administration of cholera vaccine intra-vaginally shows great mucosal reaction in female genital tract when analysed to oral administration of the vaccine.

**Vaginal Rings**

These are the circular rings known as vaginal rings. These are different type drug delivery systems which are intended to release the drug in a restrained manner after insertion in vagina. In simple vaginal rings, drug is consistently isolated with in a Polymeric ring.

This type of dosage forms or devices have certain advantages like;

- Can be controlled by the user
- It does not constrain with coitus and
- Allows nonstop delivery of microbicidal complexes.

The vaginal rings range about 5.5 cm in diameter with traverse segment diameter of 4-9 mm, where drugs are isolated constantly. At the surface of the ring the drug releases faster than the drug at the inner layer. To obtain constant and accurate release of drugs from vaginal rings two types of ring systems have been developed

- Sandwich type device
- In reservoir type device

**Sandwich device**

It consists of a slender drug containing film present beneath the superficial layer of the ring and sited between a non-medicated vital core and a non-medicated external band.

**In reservoir device**

The drugs are isolated in a central core, which is compressed by a drug free layer. Materials introduced to produce vaginal rings are polymeric in nature. Silicon devices are the most frequently used polymers for vaginal rings. Ring composed of ethylene vinyl acetate is clinically acceptable because of its greater flexibility, enhanced optical properties, greater linkage and increased impact and punch resistance [14]. The main purpose in which vaginal rings are used is for contraceptives and hormonal replacement therapy. For 21 days the ring is positioned in vagina shadowed by a week of ring permitted period in most contraceptive use. Femring and Estring are the best examples of vaginal ring projected for hormonal replacement therapy. To maintain the vaginal suppository during inclusion for proper location within the vagina plastic insertion devices are used.

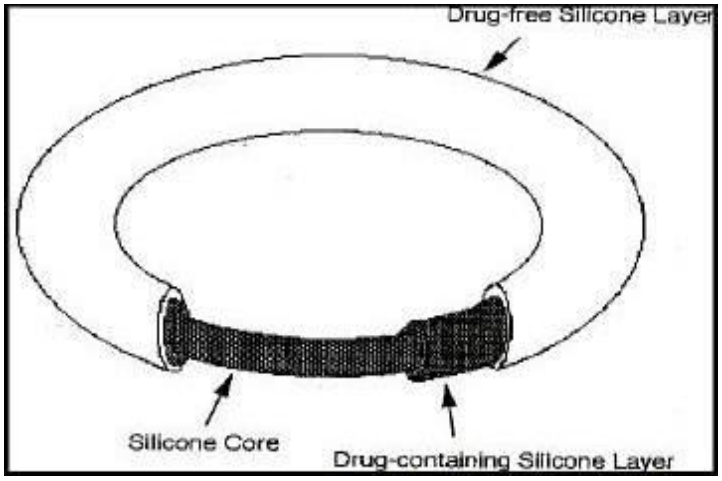
NuvaRingR is the only collective contraceptive vaginal ring available. Etonogestrel and ethinyl estradiol are the two active components present in the NuvaRingR which is flexible, transparent and contraceptive vaginal ring. 120mg/day of etonogestrel and 15mg/day of ethinyl estradiol are released over a period of 3-weeks [19]. NuvaRingR shows good response in clinical trials and is known as the effective contraceptive ring showing good cycle control and user acceptance. Femring and Estring are used in estrogen therapy as they are estrogen releasing rings. 7.5 mg of estradiol is released into the vagina when Estring is inserted which is made of silicon polymers. These rings are also used in birth control by inserting the ring into the vagina once a month to prevent pregnancy.

**Advantages of vaginal rings**

- Premenstrual symptoms (headaches/depression) and bleeding will probably be lighter and less painful
- Infection of ovaries, uterus and tubes are reduced
- Pelvic provocative disease
- Irregular/heavy periods can be controlled
- Iron deficiency anemia
- Ovarian and endometrial cancers are avoided
- Bone thinning

**Dis-Advantages**

- Vomiting and nausea
- Bleeding between periods
- Breast tenderness is caused




***Vaginal Ring.***

## NOVEL CONCEPTS IN VAGINAL DRUG DELIVERY

These NVDDS are developed and designed with desirable distribution, retention, bio-adhesion and release characters. The VDF's such as suppositories, gels, creams, foams can meet some requirements but all requirements are attained by the use of

- Bio-adhesives and
- Novel Drug Delivery Systems (NDDS)

### Bio-adhesives

These bio-adhesive molecules or formulations are capable of delivering the drug or the active agent for extended period at predictable rate. Vagina is the suitable site for bio-adhesive formulations. The predictable treatment time of fungal infection by the bio-adhesive molecules have been found to be reduced by at least 25%.It can also be used as moisturizer for dry vagina as all formulations might not necessarily contains any therapeutic agents. Tablets placed among the vaginal mucosal surfaces have been said to be the excellent bio-adhesive formulations. Polycarbophil, hydroxypropylcellulose and Polyacrylic are some of the bio-adhesive polymers which have been used for vaginal formulations. The formulation stays in the vagina for 2-3 days and upholds vagina at healthy and acidic pH.

Various peptides and proteins have also been made many attempts to administer drugs through bio-adhesive micro particulate vaginal delivery system. Dry formulations attain bio-adhesion through dehydration of local mucosa. Possessed release drug delivery systems can be accomplished by addition of time release additives. Water discemible layers are being used to deliver the drugs directly to mucosal surfaces.

### Novel Drug Delivery Systems (NDSS)

Intra-vaginal therapeutic system made from vaginally acceptable polymeric materials can be used for controlled release of drugs [9]. Phase change poloxamers show sol-gel transition in response to body temperature, pH and specific ions. This effect prolongs the residence time of dosage form in vagina. The thermoplastic polymers which can be used in manufacture of novel vaginal delivery system include plasticized nylon, plasticized polyethylene terephthalate, polyethylene and polyvinylchloride-diethyl fumarate [13]. Active volumes of progestational and estrogenic steroids which produce anti-fertility outcome over a prolonged period are released in a novel medicating method based on thermoplastic polymeric materials. Timely gelation and retention of vaginal formulations could be fundamentals in improving the drug efficacy. For the improvement of novel vaginal delivery systems (NDDS) micro emulsion based formulations which offer rapid dispersion and drug absorption profiles can be exploited. Liposomes are well known as novel vaginal delivery systems (NDDS).

## EVALUATION OF VAGINAL FORMULATIONS

The vaginal formulations are evaluated by carrying out in-vitro and in-vivo studies. Other tests for vaginal drug products include appearance, particle size, pH., dissolution rate and microbial limits basing on the dosage forms.

### In-vitro Studies

Drug discharge and bio-adhesive features are determined by the study of many physical and chemical properties of formulations. In simulated vaginal fluid the release features of a drug from vaginal formulation can be obtained and in many other dissolution media it can be determined by the vaginal dissolution tester by different types of diffusion cells. Wilhelmy plate surface technique is used to measure the strength of bio-adhesive of vaginal formulations.

### In-vivo Studies

In-vivo studies are performed on different animals to determine the effectiveness, distribution, spreading and retaining of the vaginal preparations in vagina. The most widely used techniques for the determination of effectiveness; distribution, spreading and retaining of vaginal formulations in sheep and humans are gamma scintigraphy and colposcopy. To compute the degree of coverage in vaginal vault two imaging techniques or methods have been developed. They are;

- Magnetic Resonance Imaging (MRI)
- Intra-vaginal Optic Probe

Animals like sheep, rats, rabbits, rhesus monkeys, dogs and mice are used in different studies and experimental procedures in the development of vaginal formulations. For irritation and sub-chronic testing of vaginal formulations white rabbits are widely used.

## APPLICATIONS OF VAGINAL DRUG DELIVERY SYSTEM [16]

- This is the best route for administration of drugs useful for vaginal immunization
- Multi-cycle administration of contraceptive rings
- Highly effect route of administration for treatment of HIV and fungal infection
- Effective for hormonal delivery

## CONCLUSION

In the past early years the vaginal route has remained for local application of drugs, but now it has become the most complicated route for drug administration. For resident action in the cervico-vaginal region human vagina is used. Insulin, calcitonin and sex hormones are some of the drugs imported and have been attempting to deliver these drugs through the vaginal route but the result is not successful in improvement of safe and viable vaginal formulations for these macromolecules. Intra-vaginal gels and labor inductions have been found to be the successful and potential vaginal formulations because of their bearing on childbirth. For both local and systemic drug delivery bio-adhesive formulations are possible to emerge as new vaginal formulations.

Vaginal rings play a significant role in the vaginal formulations as it possesses many advantages. Novel vaginal delivery systems overcome some key limitations associated with the conventional delivery of drugs. Vaginal route of drug administration is the major site or area for continued researches on the delivery of drugs and other microbicidal agents which can prevent the transmission of sexually transmitted diseases (STD's) and Human Immunodeficiency Virus (HIV).

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