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Review Article

Intra Vaginal Drug Delivery System: An Overview

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ABSTRACT

The human vagina represents a potential, accessible space that offers a valuable route for drug delivery through the use of specifically designed carrier systems for both local and systemic applications. Intra-vaginal drug delivery is particularly appropriate for drugs associated with women's health issues but may also have applications in general drug delivery within the female population. Vagina is one of the best routes for drugs administration like contraceptive steroids, metronidazole, anti-retroviral, etc. An intra-vaginal controlled-release drug delivery system is an effective means for achieving a continuous delivery of therapeutic agents, not only the systemically active drugs, such as contraceptive steroids, but also the locally active drugs, such as metronidazole and other drugs like Zidovudine, Lamivudine, etc. This continuous “infusion” of drugs through the vaginal mucosa can prevent the possibility of hepato-gastrointestinal first-pass metabolism gastric irritation of drugs and fluctuation of dosing interval. The advantage of intra-vaginal controlled drug administration over conventional/traditional oral administration is the drug absorbed systemically, because due to the presence of dense network of blood vessels in vaginal wall. A range of drug delivery platforms suitable for intra-vaginal administration are hydro-gels, vaginal tablets, pessaries/suppositories, particulate systems, and intra-vaginal rings.

Keywords: Vagina, First pass metabolisim, Intra vaginal drug delivery, pessaries.

INTRODUCTION

Vagina is route for administration for contraceptives, anti-fungal, and antimicrobials. It is used for the achievement of local or for systemic absorption. The vaginal wall is very well suited for the absorption of drugs for systemic use. As it contains a vast network of blood vessels[1].

This route offers certain advantages, such as avoidance of gut and hepatic first pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs. Vaginally administered agents and formulations are mainly being developed to provide "dual prophylaxis" for contraception and protection against microbial infections[2] including Acquired Immune Deficiency Syndrome(AIDS) and other sexually transmitted diseases (STDs). Drug delivery technologies that have been used for vaginal drug delivery include the intra-vaginal ring (IVR) and Vaginal Site bio-adhesive technology.

Advantages of intra vaginal drug delivery system

- Prolonged release,
- Minimal systemic side effects,
- An increase in bioavailability,
- Use of less total drug than an oral dose,
- First-pass metabolism can be avoided,
- Self medication is possible.
- Contact with digestive fluid is avoided and degradation of drug is minimized[3].
- Nausea, vomiting, emesis induced through oral administration is avoided.
- Quick onset of action.

Disadvantages

- Gender specificity,
- Patient incompliance,
- Only a few drugs are administered by this route,
- Variability in drug absorption related with menstrual cycle, menopause and pregnancy,
- Influence with sexual intercourse[4].
- Personal hygiene.
- Some drugs are sensitive at vaginal pH

VAGINAL ANATOMY AND PHYSIOLOGY WITH RESPECT TO DRUG DELIVERY

The vagina is a fibro-muscular tube approximately 10 cm in length comprised of three distinct layers namely;

- an outer adventitial layer,
- a middle muscularis layer and
- An innermost mucosal layer[5]

The vaginal rugae and micro-ridges on the epithelial cell surface permit the vagina to expand, allow the placement of vaginal formulations and increase the surface area of the vagina thus enhancing drug absorption[6].

The vagina has remarkable features in terms of vaginal secretion, pH, enzyme activity and micro-flora. These factors affect formulation spreading and retention as well as absorption and drug release in vagina.

Vaginal Secretions

The vaginal discharge is a mixture of multiple secretions that collect in the vagina from peritoneal, follicular tubal, uterine, Bartholin's and Skene's glands[7]. In presence of moisture, solid dosage formulations should ideally disperse in the vaginal canal immediately after insertion to avoid inconvenience to the users.

Enzyme Activity

The specific enzymatic activity of four different amino peptidases in vaginal homogenates decreases in the order: sheep > guinea pig > rabbit ≥ human ≥ rat[8]. The human genital tract has lower enzymatic activity leading to less degradation of protein

and peptide drugs in the vagina than the gastrointestinal tract [9].

Vaginal pH

The pH of the healthy female genital tract is acidic (pH 3.5–4.5) and is maintained within that range by bacterial conversion of glycogen from exfoliated epithelial cells to lactic acid[10].

Ideality of intra vaginal drug delivery system

- Component should melt at vaginal temperature i.e. at 36 °C,
- Intra-vaginal drug delivery device should be non-toxic and non irritating,
- It should not have any meta-stable form,
- The preparation should have wetting and emulsifying properties.
- It should have proper viscosity, so avoid the leakage of preparation from vagina (in case of semisolid dosage form),
- The preparation should have proper bio-adhesive/muco-adhesive properties, so increase the contact time between the membrane and Preparation.

FACTORS AFFECTING ABSORPTION OF DRUGS

The drug transport across vaginal membrane mainly takes place by three major ways;

- Transcellularly- via concentration dependent diffusion through the cells,
- Paracellularly- mediated via tight junctions and
- Vesicular or receptor mediated transport.

Drug absorption from vaginal delivery system is mainly takes place in two main steps:

- Drug dissolution in vaginal lumen and
- Membrane penetration.

The rate and extent of drug absorption after intra-vaginal administration may vary depending on following factors:

Physiological Factors

- changes in the thickness of epithelium layer,
- cyclic changes,
- changes in the hormones level,
- volume of vaginal fluid,
- alteration of vaginal pH and
- Sexual arousal can potentially affect drug release from any intravaginal delivery system and also alter its rate of absorption.

For e.g.

1. Vaginal absorption of steroids is affected by the thickness of vaginal epithelium [11].
2. Vaginal absorption of estrogen shows high in post menopausal women compare to premenopausal women [12].

The high volume of vaginal fluid may increase the absorption of poorly water soluble drugs; however the same condition again responsible to remove the drug from the vaginal cavity and subsequent reduction of drug absorption.

Further cervical mucus, a glycoprotein gel can possibly be exploited for bioadhesive drug delivery. However at the same time it may serve as a permeability barrier for different drug candidates[13]. Again changes in the pH of vagina will alter degree of ionization of weak electrolytic drugs and affect the release profile of pH sensitive drugs[14].

Physicochemical Factors

- Lipophilicity,
- Ionization,
- Molecular weight,
- Surface charge and
- Chemical nature can influence the vaginal drug absorption.

In consideration to permeability the lipophilic steroids like progesterone and estrone having better permeability than the

hydrophilic one like hydrocortisone and testosterone.

Vaginal & Uterine Route for Sustained/Controlled Release drug Delivery

Sustained and controlled-release devices for drug delivery in the vaginal and uterine areas are most often for the delivery of contraceptive steroid hormones. One such application is the medicated vaginal ring. Medicated vaginal rings fabricated from silastic 382 medical grade elastomer. These are of 'doughnut-shaped'. Also known as intra-vaginal rings or V-Rings.

Vaginal rings provide a means of delivering a drug to the systemic circulation at a controlled release rate.

Several vaginal ring products are currently available, including:-

- Estring - a low-dose estradiol-releasing ring, manufactured from silicone elastomer, for the treatment of vaginal atrophy.
- Femring - a low-dose estradiol-acetate releasing ring, manufactured from silicone elastomer, for the relief of hot flashes and vaginal atrophy associated with menopause.
- NuvaRing - a low-dose contraceptive vaginal ring, manufactured from poly (ethylene-co-vinyl acetate), and releasing etonogestrel (a progesterone) ethinylestradiol (an estrogen). NuvaRing - NuvaRing is inserted into the vagina and left in place for three weeks, after which it is removed for a 'ring-free' week to allow menstruation to occur.

A more common contraceptive device is the intrauterine device (IUD). Two types of medicated IUD are generally used;

- Contraceptive metals and
- Steroid hormones.

The metal device is exemplified by the CU-7, a polypropylene plastic device in shape of number 7 Copper is released by a combination of ionization and chelation from a copper wire wrapped around the vertical limb. This is effective for up to 40 m.

Application of prostaglandin containing vaginal rings for induction of labor or pregnancy termination. Anti-fungals have been important drug candidates for the treatment of gynecological conditions.

The vaginal delivery of azole anti-gungals as clotrimazole, miconazole, econazole, itraconazole and sertaconazole is effective in the topical treatment of vaginal candidiasis.

Novel concepts in vaginal drug delivery

NVDDS are designed with desirable distribution, bio-adhesion, retention and release characteristics. The conventional VDFs, such as suppositories, gels, creams and foams can meet some but not all of these requirements. Achieved by the use of

- Bio-adhesive and
- Other novel delivery systems.

Bio-adhesive delivery systems

Bio-adhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate. Bio-adhesive formulations have been found to reduce the conventional treatment time of fungal infections by at least 25%. A bio-adhesive formulation might not necessarily contain a therapeutic agent and can be used as a moisturizer for the treatment of dry vagina. Tablets that are placed directly between the vaginal mucosal surfaces have been demonstrated to be excellent bio-adhesive formulations. For example, chitosan and sodium alginate based bio-adhesive tablets were found to release 100 % of metronidazole over a period of 8 h in a buffer at pH 4.8 [17].Bio-

adhesive micro-particles have also been investigated for the vaginal delivery of salmon calcitonin using HYAFF as bio-adhesive polymer where microspheres showed increased bio-availability of drug. Water dispersible films are being used to deliver drugs directly to mucosal surfaces to form close contact with mucosal membrane [18].

Controlled release drug delivery systems can be achieved by the addition of time-release additives. Bio-adhesive formulations based on carbomers and polycarbophil give satisfactory drug delivery within the vaginal cavity following the application of a single dose. For example, Prochieve TM is a bio-adhesive gel used in hormone replacement therapy. Replens® is a muco-adhesive gel based on polycarbophil designed to be retained in the genital cavity for 3-4 days [19].

Other novel delivery systems

Phase change polymers such as poloxamers exhibit sol–gel transition in response to body temperature, pH and specific ions and they prolong the residence time of the dosage form in the vagina. Formulations based on a thermoplastic graft copolymer have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins in a vaginal environment.

An intravaginal therapeutic system made from certain vaginally acceptable thermoplastic polymeric materials that are not absorbable can be used for the controlled release of drug. One preferred example of a thermoplastic polymer is styrene-butadiene block copolymer. Additional thermoplastic polymers that can be used for manufacturing novel vaginal delivery systems include polymethylacrylate, polybutylmeth-acrylate, plasticized polyvinylchloride, plasticized nylon, plasticized polyethylene-terephthalate, polyethylene, polyacrylonitrile, polytrifluoro chloroethylene, poly-4,4'-isopro-pylenediphenylene carbonate, polyethylene-vinyl esters and polyvinylchloride-diethyl fumarate. A novel medicating system based on thermoplastic polymeric materials releases effective amounts of progestational and estrogenic steroids, which produce a desired anti-fertility effect over a prolonged period. Chang *et al.* have recently reported a muco-adhesive thermo-sensitive gel that exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation [20].

Vaginal Dosage Forms

In the development of vaginal dosage forms, several considerations should be addressed as:-

- Maintenance of an optimal pH for vaginal epithelium,
- Ease of application,
- Even distribution of the drug,
- Retention time in the vagina,
- Compatibility with co-administered medicines.

Many different types of formulations have been applied vaginally as-

- Vaginal Tablets,
- Vaginal suppositories or pessaries,
- Vaginal Foams, douches(are aqueous solutions that are administered into the vagina for
- Cleansing purpose), sprays, gels, creams(as vehicles for drugs such as anti-infective or contraceptive agents) and
- Vaginal rings

Tablets and Suppositories

A large number of intravaginal delivery systems are also available in the form of tablets and suppositories. Some authors use the terms pessaries and suppositories interchangeably and consider vaginal tablet as a separate dosage form.These formulations are designed to melt in vaginal cavity and release the active constituent over prolong period of time.Vaginal suppositories intended for localized effects are employed mainly as contraceptives, antiseptics and anti-fungal.

Suppository systems are most commonly used to administer drugs like dehydroepiandrosterone sulphate for ripening effect on uterine cervix, miconazole for vaginal candiasis and progesterone for hormonal replacement therapy.Normal vaginal tablets contain similar components as like conventional oral tablets, they are easy to manufacture and insertion.Drugs that are administered as vaginal tablets include itraconazole, clotrimazole, metronidazole and prostaglandins. Mucoadhesive polymers are sometimes used in vaginal tablet formulation to increase the vaginal residence time.The polystyrene sulfonate (PSS) is also shows superior antimicrobial activity against HIV and HSV, therefore it is formulated in the form of vaginal tablet, which will not immobilize sperm, not cytotoxic and did not inhibit normal vaginal flora, so as proved as potential delivery system [27]. Literature shows that presence of hydrophobic and release retarding materials may decrease the absorption of a drug from a vaginal formulation and too hydrophobic drugs may not be suitable for vaginal tablets. Further presence of penetration enhancers such as surfactants, bile salts can significantly enhance absorption.

Creams and Gels

A number research work has been done on creams and gels as an intravaginal delivery system. They are mainly used for topical delivery of contraceptives and anti bacterial drugs. These delivery systems are messy to use, uncomfortable, may not provide an exact dose because of non-uniformity and leakage.Metronidazole and clindamycin vaginal creams for the treatment of bacterial vaginosis already proved them as efficacious as oral delivery.Recently a gel microemultion based formulation of spermicide with anti HIV effect of zidovudine has been developed [28].Literature shows that minocaprin hydrogel formulations possess potent microbicidal activity against HIV, HSV, *Chlamydia trachomatis* and *Neisseria gonorrhea*, which is less cytotoxic than nonoxynol-935[29].Cellulose acetate phthalate (CAP) used the pharmaceutical industries as enteric coating agent but recent study focused that it's having an potency to absorb and inactivate HIV-1, HSV and other STIs [30]. Further utilizing this ability of CAP a potential anti-HIV vaginal gel formulation has been formulated that are under phase II clinical trials [31].An Intravaginal vaccine delivery by means of vaginal gel is also reported, even intravaginal delivery of cholera vaccine showed a greater mucosal response in female genital tract compare to oral administration of the vaccine [32].Further oxytoscin, dinoprostone and misoprostol commonly used for cervical ripening and induction of labor are also available in vaginal gel form.

Vaginal Rings

Vaginal rings are circular ring type drug delivery devices designed to release drug in a controlled release fashion after insertion in the vagina.

This type of device having several advantages like,

- It can be controlled by the user,
- Does not interfere with coitus and
- Allows continuous delivery of microbicidal compounds.

They are 5.5 cm in diameter with a circular cross section diameter of 4-9 mm, where drugs are homogeneously dispersed. Drugs at the surface of the ring release faster than the drug in the inner layer. The key challenge behind the development of this type of device is finding the optimum dose that will deliver the least amount of drug necessary to ensure protection. To obtain constant release of drug from vaginal ring sandwich or reservoir types of system have been developed.

Sandwich type devices consist of a narrow drug containing layer located below the surface of the ring and positioned between a non medicated central core and a non-medicated outer band.

In reservoir type of rings, drugs are dispersed in a central core, which is than encapsulated by a drug free layer. The materials introduced to fabricate vaginal ring are mainly polymeric in nature.

As per literature most commonly used polymers for vaginal ring are ploy (dimethylsiloxane) or silicon devices, other elastomeric polymers such as ethylene vinyl acetate have been tested in recent years [33]. Clinical acceptability of ring made up of ethylene vinyl acetate is very high because of its increase flexibility, improved optical properties, greater adhesion and increased impact and punch resistance [34].Vaginal rings mainly used for contraceptive and hormonal replacement therapy. For most contraceptive application the ring is placed in vagina for 21 days followed by a week of ring free period. Nuvaring is one of the examples of contraceptive ring available in US market [35].Further Femring and Estring are the example of vaginal ring intended for hormonal replacement therapy, release estrogen.

Literature reported that dapivurine, which is also known as TMC120, is a potent non-nucleoside reverse transcriptase inhibitor that is the only vaginal ring system used as an intravaginal microbicide delivery system for preventing the transmission of STIs and HIV[36].

Plastic insertion devices are usually used to hold the vaginal suppository during insertion for proper placement within the vagina.Design of a liposome delivery system for vaginal administration of acyclovir was investigated, to provide sustained release and improve bioavailability of the encapsulated drug for the local treatment of genital herpes.

EVALUATION OF VAGINAL FORMULATIONS

A vaginal formulation must be evaluated by performing both *in vitro* and *in vivo* studies. Depending on the dosage form, additional tests for vaginal drug products may include appearance, viscosity, pH, particle size analysis, dissolution rate, content uniformity and microbial limits [37].

In vitro studies

In vitro studies include the determination of drug release and bio-adhesive characteristics in addition to various physical and chemical properties of formulations .The release characteristics of a drug from a vaginal formulation can be determined in simulated vaginal fluid (pH 4.2) and in various dissolution media (pH range 2–12) by different types of diffusion cells with certain modifications and a vaginal dissolution tester .The bio-adhesive strength of the vaginal formulation can be measured by various techniques (like Wilhelmy plate surface technique) [38].

In vivo studies

In vivo studies are conducted in different animal models to assess efficacy, distribution, spreading and retention of formulations in the vagina [39].Gamma scintigraphy and colposcopy [40] are desirable techniques for assessing the distribution, spreading and retention of vaginal formulations in sheep and humans. However, the significance of these findings is debatable.

Two imaging techniques are being developed to measure the degree of coverage in the vaginal vault: magnetic resonance imaging (MRI) and an intravaginal optic probe[41]. Several animal model such as sheep, rats, rabbits, rhesus monkeys, macaque monkeys, dogs and mice have been used in different studies in the development of vaginal formulations [42]. White rabbits are used for primary irritation and subchronic toxicity testing. Recently developed vaginal-ectocervical (VEC) tissue models will serve as useful, highly reproducible, non-animal tools to assess the irritation due to vaginal care product [43.]

APPLICATIONS OF INTRA VAGINAL DRUG DELIVERY SYSTEM

- This route of drug administration is useful for vaginal immunization,
- Multi-cycle administration of vaginal contraceptive rings,
- Effective route for the treatment of HIV infection,
- Effective route for the treatment of local fungal infection,
- Effective for the delivery of hormones.

CONCLUSION

The vaginal route has been used for the local application of drugs, but is now becoming a potential route for noninvasive, controlled trans-mucosal delivery of both local and systemic therapeutically active compounds.Novel vaginal delivery systems overcome some of the key limitations associated with conventional delivery of vaginal drugs. Vaginal drug delivery is a promising area for continued research on the delivery of microbicides that can prevent transmission of sexually transmitted diseases and HIV.

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Table 1. Influence of Age on the variation of pH, Length, and Width of human Vagina[15, 16]

Changes of vagina	pH	Length of vagina (cm)	Width of vagina(cm)
Before puberty	**7**	**4.5-6**	**1-1.5**
Reproductive age	**4-5**	**10**	**2.5**
Adult pre-menopause	**4-5**	**7-8**	**2**
Post-menopause	**4-7**	**4.5-6**	**1-1.5**

Table 2. Various dosage forms in vaginal drug delivery system

Drug	Formulation	Polymers	Purpose of Investigation	Ref
Insulin	Microspheres	HYAFF	Increased absorption from HYAFF microsphere compared to aqueous solution of the drugs	21
Metronidazole	Tablet (Bioadhesive)	Chitosan, Sodium Alginate	Mucoadhesive dosage form	22
Clotrimazole	Pessaries	Polycarbophyl, HPMC Hyaluronic sodium salt	Good adhesion properties and capacity to hold the dosage form in the target site	23
Acyclovir	Liposomal hydrogel (Bioadhesive)	Carbopol 974P	Sustained release and improved bioavailability	24
Progesterone	Vaginal ring	Polydimethylsiloxane	Advanced delivery system of hormone replacement in females	25

Table 3. Commonly used marketed vaginal products [44]

Therapeutic Drug (Brand Name)	Intended Use	Dosage Form	Comments	Company
Nonoxynol-9	Contraceptive	Vaginal gel	Bioadhesive in Nature.	Columbia Laboratories.
Etonogestrel, ethinyl estradiol (NuvaRing ®)	Contraceptive	Vaginal ring	Commonly reported adverse events are vaginitis, weight gain	Organon
Clotrimazole (Trivagizole®)	Anti-fungal	Cream	Minor skin irritation	Taro Pharmaceuticals
Metronidazole (Metrogel Vaginal®)	Bacterial vaginosis	Vaginal gel	Vaginal discharge.	3M Pharmaceuticals
Estradiol (Vagifem®)	Atropic vaginitis	Vaginal tablet	Mild allergic Reaction.	Novo Nordisk
Estradiol (Estring®)	Hormone therapy	Vaginal ring	Can increase the vaginal secretion	Pharmacia and Upjohn
Tioconazole (Trivagizole®)	Tioconazole (Trivagizole®)	Vaginal ointment	Possible side effects are swelling of face, Lips, tongue.	Bristol Myers Squibb

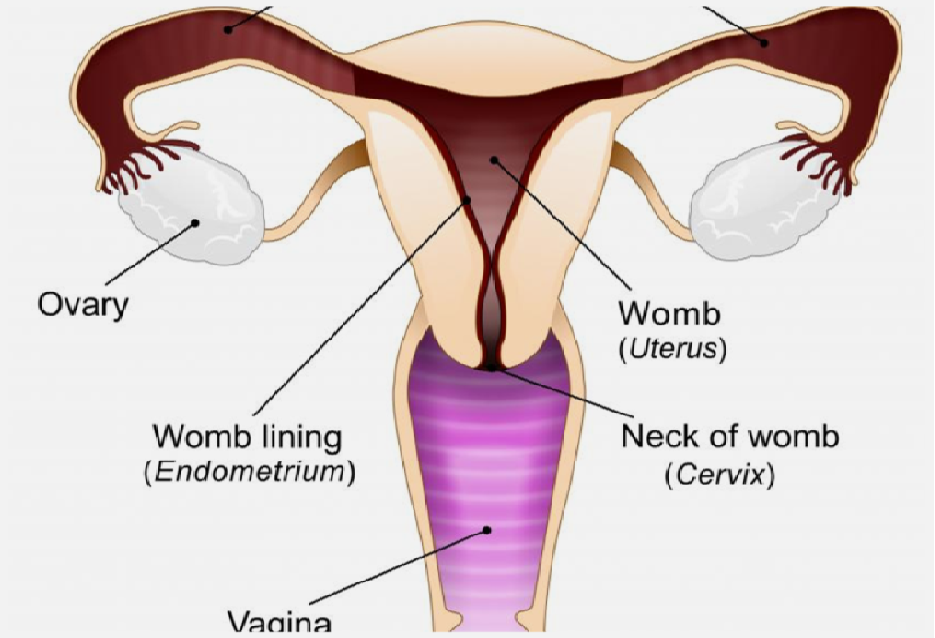

Figure.1. Structure of female reproductive system