Intra Vaginal Drug Delivery System (Novel Drug Delivery System)

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ABSTRACT

In case of intra-vaginal route of drug administration the dosage form is applied vaginally for the convenient release of the dosage form and for better therapeutic action of the medicament, it is usually used in HIV patients. Many conditions affect the female reproductive tract, such as sexually transmitted diseases, fungal & bacterial infections, cancer and various pathogens such as virus (human immunodeficiency virus, HIV), bacteria (Gardnerella vaginalis), fungi (Candida spp.) or parasites (Trichomonas vaginalis). Systemically active drugs (contraceptive steroids) as well as locally active drugs (metronidazole, Zidovudine, Lamivudine) can be effectively delivered for an extended period of time by the help of intra-vaginal controlled release system. Continuous infusion of drugs through vaginal mucosa results in the reduced possibilities of hepatic gastrointestinal first-pass metabolism, gastric impatience of drugs and vacillation of dosing interval. Current study focus on the, use of various polymers which are used in hydrogels, these polymers provide bioadhesive property to the vaginal formulations, so that the vaginal formulation remains on vaginal tissues for 3-4 days. Currently available vaginal dosage forms have several limitations, such as leakage and messiness necessitating the need to develop novel drug delivery systems.

Keywords: VDDS, LHRH, vaginal immunization, bioadhesion, HYAFF.

I. INTRODUCTION

In vaginal drug delivery system the drug is delivered directly into the vaginal cavity. This is an important route of drug administration by which systemic and local both effect can be achieved. Vaginal drug delivery is very effective for the treatment of vaginal infections. This system is also utilized for the delivery of contraceptive. The first vaginal formulation developed for the treatment of local inflammation, bacterial and fungal infections. This route is more effective than parenteral for some drugs such as oxytosin, calcitonin, propranolol, LHRH agonist, human growth hormone and steroids used in hormone replacement therapy or for contraception. The first vaginal controlled drug delivery system was designed in 1970, which was a vaginal ring used for delivery of medroxy progesterone acetate for contraception. Age, cyclic hormone changes, and sexual activity may influence the composition, volume, pH and viscosity of the vaginal fluids, hence the action of vaginally applied drug delivery systems or dosage forms may affected or altered. Presence of any infection or pregnancy may also interrupt the desired activity of drugs.

Advantages of Intra vaginal drug delivery system

- Effective for hormonal delivery
- Extended release of drug
- Reduced systemic side effect
- Enhanced bio-availability
- Effective for orally inactive drugs
- Quick onset of action
- Self medication is possible
- Digestive fluids are bypassed and degradation of drug is minimized

Dis-Advantages of intra vaginal drug delivery system

- Gender Specificity
- Patient incompliance
- Sometimes leakage of drug from vagina and wetting of under garments
- Variability in drug absorption related with menstrual cycle, menopause and pregnancy
- Influence with sexual intercourse
- Personal hygiene
- Some drugs are sensitive at vaginal pH

Anatomy and physiology of the vagina

The vagina is an organ of the female reproductive tract. It is a distensible muscular tube which extends posteriorly from the external vaginal orifice to the cervix. Female sexual physiology was for the first time described in Dickinson's textbooks in 1949 and subsequently by Masters and Johnson. The vagina is situated between the rectum, urethra and bladder, and is the gateway from the vulva, the outer genitalia, to the cervix, the opening of the uterus, which is a central organ of the reproduction in a female. Vagina is a muscular tube which lengths about 6-10cms long approximately extending from the cervix of the uterus. The surface of the vagina is composed of numerous folds, which are often called rugae. The rugae provide dispensability, support and an increased surface area of the vaginal wall. Drugs absorbed from the vagina does not undergo first-
pass metabolism because blood leaving the vagina enters the peripheral circulation via a rich venous plexus, which empties primarily into the internal iliac veins[15]. 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.

During menstrual period because both the ejaculate and vaginal transudate are alkaline in nature, hence vaginal pH increases. Age, health conditions Secretions from the endometrium and fallopian tubes may also alter the vaginal pH. Women of reproductive age produce fluid at a rate of 3–4 g/4 h, while the discharge produced by postmenopausal women is reduced by 50% compared to that produced fluid may contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl ketones and aromatic compounds. Sexual arousal may affect the volume and composition of vaginal fluids and that can alter the drug release pattern from the vaginal delivery system.

**Histology of the Vagina**

The vagina is composed of four histological layers (internal to external):

1. Stratified squamous epithelium – this layer provides protection and is lubricated by cervical mucus (the vagina itself does not contain any glands).
2. Elastic lamina propria – a dense connective tissue layer which projects papillae into the overlying epithelium. The larger veins are located here.
3. Fibromuscular layer – comprising two layers of smooth muscle; an inner circular and an outer longitudinal.
4. Adventitia – a fibrous layer, which provides additional strength to the vagina whilst also binding it to surrounding structures.

**Vaginal Anatomy and Physiology with Respect to Drug Delivery**

The inner epithelial layer of vagina contains numerous rugae and micro-ridges which allow it to expand and increases surface area, thus the vaginal formulations can be easily placed into the vaginal cavity. 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 secretions from peritoneal, follicular tubal, uterine, Bartholin’s and Skene’s glands are discharge from the vagina as a mixture.[24]

**Vaginal pH:** The vaginal pH of healthy women of reproductive age is acidic (pH 4–5); which is maintained by lactobacillus convert glycogen from epithelial cells to lactic acid. The vaginal pH should be controlled for successful vaginal delivery of drugs.[20]

**Cyclic changes:** The changes in hormone levels (especially estrogens) during the menstrual cycle Secretions may also impart with vaginal formulation.

**Vaginal Infections**

Gynecological infections can be located at the level of vulva or internally in the vagina, cervix, uterus and fallopian tubes. The most common of infectious vaginitis are bacterial vaginosis (22-50%) [33].

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Figure 1.1: Internal structure of vagina
vulvovaginal candidiasis (17-39%) and trichomoniasis (4-35%) [18]. Bacterial vaginosis, candidal, trichomonal and Gonococcal vaginal infections are a major health problems associated with gynecologic complications and increase in replication, shedding and transmission of HIV and other STIs in women of reproductive age.

Factors affecting the vaginal absorption of drug

The absorption of drug across vaginal membrane takes place mainly by three mechanism:

1. Transcellularly- via concentration dependent diffusion through the cells
2. Paracellularly- mediated via tight junctions
3. Vesicular or receptor mediated transport

There are mainly two steps involved in the absorption of drug from vaginal delivery system:

1. Drug dissolution in vaginal lumen
2. Membrane penetration

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

Physiological Factors

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

For eg,

1. Poorly watersoluble drugs easily absorb if vaginal fluid volume is high.
2. In post menopausal women estrogen is rapidly absorb than pre menopausal women.
3. Vaginal absorption of steroids is affected by the thickness of vaginal epithelium.

However the same condition again responsible to remove the drug from the vaginal cavity and subsequent reduction of drug absorption.

Physicochemical Factors

- Lipophilicity,
- Ionization,
- Molecular weight,
- Surface charge and
- Chemical nature of the drug can also affect the vaginal absorption. Lipophilic steroids (progesterone and estrone) easily permeable through vaginal membrane than hydrophilic (hydrocortisone and testosterone).

II. IMPROVEMENT OF VAGINAL ABSORPTION

Drugs having the poor vaginal absorption can cause poor membrane permeability due to molecular size, lack of lipophilicity, fluid volume, estrus cycle and pH of vagina. To solve this problem, most studies have been reported the use of penetration enhancer to facilitate the transport of these molecules and improve the bioavailability. Generally enhancers used for this purpose work by one or combined mechanism of the following –

- By increasing intracellular transport or use of penetrating agents e.g. PEG.
- By increasing the contact time between the dosage form and the vaginal membrane by using mucoadhesive polymers e.g. Carbopol 934, 940, 973 and formulation of gel and by increasing viscosity of formulation.
The new type of vaginal controlled system bioadhesive formulation are also effective for absorption enhancement in systemic as well as topical application.

An increase in the concentration gradient across the vaginal mucosa, by increasing vaginal blood flow, may improve absorption of drug.

Chelating agent are used in vaginal formulation as penetration enhancer to improve drug absorption. Absorption of protein leuprolide is improved when penetration enhancer such as carboxylic acid with chelating property are co-administered.

By the use of pro-drugs enhances drug permeability through modification of the hydrophilicity or lipophilicity of the drug.

**Novel concepts in vaginal drug delivery**

NVDDS are developed to achieve desirable distribution, bio-adhesion, retention and release characteristics. All of these requirements can not be fulfilled by the conventional vaginal formulations like suppositories, gels, creams and foams. Bioadhesive and other novel delivery systems are developed to achieve these features. 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).

**Bio-adhesive delivery system**

These formulation deliver the active agent for an extended period in determined Manner. These formulation have been shown to direct the treatment time of fungal infection by approx 25%. such formulation need not contain any API but can be Utilised as moisturizer for treating of dry vagina. Excellent bio adhesive formulation in the form of tablet which are placed directly between the vaginal mucosal surfaces have been successful. Researcher have also searched bio adhesive micro particle, for vaginal delivery of Salmon calcitonin using HYAFF as bioadhesive polymer were increased bioavailability of drug was shown by micro spheres. It is possible to achieve controlled release drug delivery by adding the time release additives. an excellent Drug Delivery is seen with in the vaginal cavity by the bio adhesive formulation based on carboxomers and polycarbophil

**Other novel delivery system –**

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. To deliver the extended release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins in a vaginal cavity can be attain by the use of Formulations based on a thermoplastic graft Copolymer.

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 polyethylenechloroethylene, polyethylenevinylacetate, polyvinylchloride, plasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneetherphthalate, polystyrene, polyacrylonitrile, polytrifluorochloroethylene, poly-4,4’-isopropylenediphénylene carbonate, polyethylenevinyl esters and polyvinylchloride-diethyl fumarate.

**Classification of Intra-Vaginal Drug Delivery System**

1. Vaginal rings
2. Vaginal powder
3. Vaginal Capsule
4. Vaginal Ointment
5. Vaginal gel and creams
6. Suppositories and Tablets
7. Vaginal films
8. Vaginal aerosol

**1. Vaginal ring**

These are polymeric drug delivery device designed to provide controlled release of drugs intravaginaladministration over an extended period of time. The resident means are inserted into vagina. Has things size approx 5.5 cm diameter with cross section is 4.5 mm the Wreck of proper dispersed in a polymeric ring. Jug at surface of the ring is release faster than drug in the inner layer of the Ring. Sometimes outer most layer of ring provide initial brust.

The rate of drug release modified by change core diameter of thickness of the No of medicated coating.Veginal ring used in Contraceptive and hormone Replacement therapy, mainly Contraceptive. Ring are placed in vagina for 21 days followed by a week of ring free period .There will even in US market Nuvring. Bhejna ringtone content to active component, Oestrogenand progestrone, vaginal ring release 120 mg/day.

**They are following types**

**Reservoir types**

In this type of ring drug are dispersed in a central core, which is encapsulated by a drug-free layer.

**Sandwich type**

This type device consists of narrow drugs containing layer located below the surface of the ring and positioned between a non medicated outer based

**Combined contraceptive ring**

Consist of major Reservoir and minor reservoir and glass closer they help to release a combination of hormone therapy and contraceptive, simultaneously.

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2. **Vaginal powder**

The vaginal powder used in antifungal and antibacterial infection, and it’s also prevent the breeding of fungal infection and bacterial in vaginal area. They are prepared by dissolving hydroxypropyl cellulose in H2O with heat specific temperature, slightly cooled and the Bisphophonate is add. The mixture is known as Lyophilized.

3. **Vaginal capsule**

These are the combination medicine that is prescribed to treat various type of vaginal infection associated with vaginal discharge. It's fight Against infection by prevent the growth of infection causes microorganism. The skilled artisan will appreciate that various modifications, substitutions, Omissions and additions may be made without departing from the spirit thereof.

4. **Vaginal ointment**

Vaginal ointment according to researcher ointment are prepared by Oil and Aqueous phase. Into the ointment Base the drug art selected from the group of compound consist of clodronate, Tiludronat, Alendronate, and oil phase added simultaneously Both phase are continuously mixed with etidronate,ibandronate, neridronate, zoledronate, is dissolve in the aqueous phase and oil phase and Aqueous are properly mixed.

5. **Vaginal Creams and gel**

These are used for topical delivery of contraceptive and antibacterial drug. These are uncomfortable to use may be not provide adjust amount dose which is required. Metronidazole and clindamycin are used in the treatment bacterial vaginosisis.Micro-encapsulation gel developed recently of this use (sperrmicide and Anti HIV effect ofZidavodine ) cellulose acetate phthalate CCAP) used as coating agent,but it has to potency to absorb Inactive HIV-1, HSV and other STIs .CAP a Potential anti -HIV .Vaginal gel are made under phase II clinical trails due to its efficacy. Intravaginal delivery of Cholera vaccine Shown greater mucosal response in female to oral administration vaccine.

6. **Suppositories and tablet**

Suppositories and vaginal tablet are designed to melt in veginal cavity and release it API. Suppositories generally used in Contraceptive, Antiseptic, and anti-fungal, Dhydroepinandrosteronesulphate is mainly used in suppositories (as constituents. Which work for the ripening effect on uterinecervix, miconazole for vaginal candidasis and progestere for hormonal replacement therapy? Itraconazole, clotrimazole, metronidazole and prostaglandins are the drug which are used vaginal tablet. (mucoadhesive polymers are sometimes used in vaginal tablet)The polystyrene sulfonate (PSS) is Show anti microbial activity against (HIV and HSV). That's why it is formulated in veginal tablet. Its function is to immobilized sperm not cytotoxic and did not inhibit normal vaginal flora, so as proved as potential delivery system.
7. Vaginal Film (VCF)  
These are the polymeric Drug delivery system the shape of film are square and thin seat, usually range from 220 to 240 micro m in thickness. These seat are - square approximately 5cm* 5cm and colorless and soft, presenting a Homogenous surface.

8. Vaginal Aerosol  
These are the recent marketed formulation aerosol containing estrogenic substance and contraceptive agent in the Foam. Aerosol container has plunger which apply the form in the vagina cavity. Novel approaches bioadhesive foam market formulation are povidone – iodine vaginal Foam.

III. IDEAL PROPERTIES OF INTRA-VAGINAL DRUG DELIVERY SYSTEM

1) Component should melt at vaginal temperature i.e. at 36 °C.
2) Intra-vaginal drug delivery device should be non-toxic and non-irritating.
3) It should not have any meta-stable form.
4) The preparation should have high water number.
5) The preparation should have wetting and emulsifying properties.
6) The preparation should be non-sensitized on vaginal pH (i.e. 3.5-4.9)5
7) It should be stable on storage.
8) The preparation should have small interval between melting and solidification point.
9) The preparation should have proper viscosity, so avoid the leakage of preparation from vagina (in case of semisolid dosage form).
10) The preparation should have proper bio-adhesive/mucoadhesive properties, so increase the contact time between the membrane and preparation [9].

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 limit.

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 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.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.
- **Intra-vaginal probe method**- an intra-vaginal probe method made up of 18 independent fiber-optic pressure transducers positioned along its upper and lower blades. The probe reliably detected the integrity of the vagina wall and support structures as an integrated functional unit.

Table 1.1: Commonly used marketed vaginal product

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Therapeutic drug</th>
<th>Dosage form</th>
<th>Intended use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynelotrimine</td>
<td>Cotrimazole</td>
<td>Cream</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Terazole 3</td>
<td>Terconazole</td>
<td>Cream</td>
<td>antifungal</td>
</tr>
<tr>
<td>Gynazole</td>
<td>Butoconazole</td>
<td>cream</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Trimo san</td>
<td>Hydroxyquinoline</td>
<td>Jelly</td>
<td>Maintain pH &amp; bacterial growth</td>
</tr>
<tr>
<td>Clindesse</td>
<td>Clindamycin</td>
<td>Cream</td>
<td>bacterial vaginosis</td>
</tr>
<tr>
<td>Vandazole</td>
<td>Metronidazole</td>
<td>Gel</td>
<td>Bacterial infections</td>
</tr>
</tbody>
</table>
Application of 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.
- Vaginal route is suitable for the treatment of local fungal infection.
- Hormones can be delivered effectively by this route.

Vaginal Immunization

Many successful immunization with DNA vaccine have been administered through the various mucosal route for many pathogens. A vaginal route has several significant site of entry. Since a majority of conventional vaccines are administered via the oral or parenteral route, this confers systemic immunity instead of the mucosal immunity. Researcher are continuously studying a single vaccine formulation against a wide variety of pathogen including the human immunodeficiency virus (HIV), it has been reported that development of a Nova HIV, CCR5 receptor, vaccine for the control of mucosal Simian (SIV) and human form of virus. In female rhesus monkey the vaccine was ing a single vaccine formulation against a wide

IV. CONCLUSION

An analysis and understanding of the available treatment strageties for various vaginal afflictions led us to devising a model formulation based on strategies to overcome the physiological challenges offered by the target site. The purported formulation bearing SLNs loaded with itraconazole offers to assimilate itself in the vaginal milieu with prolonged muco-retention, high tolerability, and enhanced antifungal efficacy. 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). Present review supports the vaginal route as an acceptable and even preferable method for drug delivery, particularly for hormones, whether for contraception or postmenopausal estrogen therapy. Present review supports the vaginal route as an acceptable and even preferable method for drug delivery, particularly for hormones, whether for contraception or postmenopausal estrogen therapy.

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