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| Vaginal Drug Delivery |
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***VAGINAL DRUG DELIVERY***

**Introduction**

Vaginal dosage forms have been developed and used clinically for many years in local therapy. Pharmaceutical dosage forms available for intravaginal delivery consist primarily of those used to treat specific gynecological conditions. Products available include vaginal contraceptives, antifungals, antimicrobials, cleansers, deodorants, and lubricants. These products are formulated as tablets, creams, suppositories, foams, films, solutions, ointments, and gels. Currently, numerous medications intended only for local activity in the vagina are available through prescriptions or over-the counter (OTC). The rich vasculature of the mucosa makes this an attractive route for systemic drug delivery providing direct entry to the blood stream, thus bypassing the hepatic portal system. Several pharmacologically active compounds, that are metabolized extensively when taken orally, such as progesterone and estrogen, have been delivered intravaginally for achieving their systemic activity. Use of the vaginal route as a novel site for drug delivery has recently received greater attention, particularly with new therapeutic agents that are subject to extensive hepatic “first-pass” elimination, such as therapeutic proteins and peptides.

**Vaginal Anatomy and Physiology**

The vagina is a canal extending from the vulva to the cervix. Physiologically, the vagina serves as a conduit for the passage of seminal fluid, an excretory duct for menstrual discharge, and as the lower part of the birth canal. The vagina is characterized by an exceptional elasticity, having the greatest resiliency at parturition. Changes in the cytology of the vaginal epithelium occur with the cyclical stages in women. The epithelium is thickest in the proliferative stage, peaking at ovulation, and then diminishing with the secretory phase.

During menopause, the epithelium becomes markedly thinner and is often invaded with leukocytes. Glycogen is very low or completely absent, contributing to the change in vaginal microbiology and pH. Vaginal secretions become scant and watery, and the pH increases from 4.5-5.5 to 7.0-7.4. Resistance to bacterial and fungal infections is reduced due to the lower population of acidophilic organisms which convert glycogen to lactic acids.

**Vaginal Absorption**

The vaginal delivery of estrogen and progesterone has been well documented over the years and used clinically in dosage forms, such as vaginal creams and suppositories. Vaginal absorption of drugs is dependent upon such physicochemical properties as molecular weight, lipophilicity, ionization, molecular size, chemical nature, and local action. The thickness of the vaginal wall (affected by the ovarian cycle or pregnancy), changes in the vaginal epithelium and change in pH (with menopause) also affects vaginal absorption of drugs. Prior to absorption, drugs must be in solution. The fluid present in the vagina can help dissolve drugs, but the cervical mucus secretion also can present a barrier. A drug can also be removed when cervical mucus is in abundance. Dosage forms can undergo different absorption patterns due to the differing dissolution patterns in vaginal fluid. Thus, dissolution of a drug can be a rate-limiting step for systemic absorption and is of particular concern for poorly soluble drugs. This issue is less important if the drug is dissolved in an aqueous gel or solution rather than delivered as tablet or suppository. The vaginal epithelium does exhibit some (although limited) enzymatic activity thus, deactivation of some drugs by these enzymes could be problem.

**Permeability**

Transport across the vaginal membrane can occur by three primary pathways: transcellular route, the intercellular route, and the vesicular route. With the transcellular route diffusion occurs through the cell due to a concentration gradient. Diffusion occurs through spacing between cells in the intercellular route and vesicular is via receptor-mediated transport (through vesicles).

**Advantages and Disadvantages of Vaginal Administration**

1. The vaginal route can be used for both local and systemic administration.
2. Avoidance of the presystemic elimination associated with oral dosage forms.
3. Convenience of self-administration and removal.
4. Patient compliance
5. Continuous drug administration (long acting drug delivery system e.g in Mirena IUD ( levonorgestrel-releasing intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir around a vertical stem designed to prevent pregnancy for up to 5 years.(Fig 1)
6. Absorption is not affected by GI disturbances.
7. Lower doses of hormones can be delivered by this route to achieve a local effect, and this reduces the potential for systemic side effects.

**Disadvantages:**

1. The thickness of the vaginal epithelium and the pH vary with age, hormonal activity, and the menstrual cycle. This influences the permeability of drug molecules and hence the extent of absorption. Systemic absorption can be erratic or unpredictable or undesirable (when used for local effect).
2. Formulation may leak out ( gels or solution) or slip out (suppositories/pessaries).
3. Drug or other formulation ingredient can cause local irritation.
4. Compliance issue for patients who are reluctant to use vaginal route of drug administration.

**Delivery Systems**

1. ***Tablets( Inserts):***

Vaginal tablets are stable and less messy to handle than creams or ointments. The tablets have a special shape for easy insertion (often diamond-shaped). Frequently a plastic applicator is used to insert the tablet. The tablets are intended to disintegrate within the vagina and then release the drug. They offer the advantage of ease of manufacture and insertion. Vagifem® is a vaginal tablet that contains estradiol and is indicated for the treatment of atrophic vaginitis. The estradiol is released locally without resulting in any appreciable increase in systemic estradiol concentrations or estrogenic side effects. In the tablet, estradiol is distributed in a hydroxypropylmethylcellulose matrix, which helps the tablet to adhere to the vaginal epithelium, slowly hydrate, and then release the drug.

1. ***Suppositories (pessaries) :***

Suppositories are also termed pessaries. They are usually oviform or cone shaped. They release the drug by melting at body temperature (37oC) or dissolving in body fluids. Polyethylene glycol (PEG) is the most commonly used pessary base.

1. ***Creams, Ointment, Gels, and Foams:***

They are generally used to provide a local action in the vagina.These are most commonly used for the delivery of spermicides, antibacterial drug, hormones, and drugs used for cervical ripening. These products are sometimes messy to use and can be uncomfortable because they tend to leak out of the vagina. Vaginal foams contain propellants that aid in the delivery of the drug. Desired drug concentration can only be maintained for a very short time with that repeated application is required because creams, ointments and gels tend to be washed away by vaginal fluids. An increased interest is in formulating those by using mucoadehsive vehicles thus increasing residence and contact time of the formulation.

1. ***Vaginal Rings:***

Vaginal rings provide a means of delivering a pharmacologically active agent to the systemic circulation at a controlled rate. The vaginal rings developed to date are primarily used for contraception. Compounds delivered include medroxyprogesterone acetate (MPA), estradiol, norgestrel, levonorgestrel, combinations of progestins and estradiol, and combinations of progesterone and estrogens.

Vaginal rings have been shown to be safe and effective for the delivery of estradiol and have been found to be more comfortable than a pessary. Vaginal rings are made of biocompatible silicone elastomers that consist of a drug-free core ring and a drug-containing coat. Vaginal rings are inserted and positioned around the cervix. Those designed for contraception are kept intravaginally for 21 days and removed for 7 days to allow for menstrual flow. The new generation, sandwich-type vaginal rings contain a drug-dispersed silicone polymer matrix which is coated by a non-medicated silicone polymeric membrane. The design reduces the initial spike of drug release frequently observed in the first treatment cycle of vaginal rings for contraception. The concept of intravaginal dual administration of progestin and estrogen in combination was recently extended to the development of a combined contraceptive vaginal ring. This new design is constructed from two drug reservoir compartments; the major compartment consists of a 3-keto-desogestrel loaded core, and the other, minor compartment consists of a core loaded with a combination of 3-keto-desogestrel and ethinylestradiol, a synthetic estrogen. These drug reservoir compartments are separated by two steroid-impermeable glass closures, as the partitions, and release the steroids at a fixed ratio occurs through a rate limiting silicone membrane.

**Fig 1: Mirena intrauterine Drug Delivery Device**

