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Review Article

Vagina as an application site for drug delivery

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ARTICLE DETAILS	ABSTRACT
	The vagina, distinct than other systems like buccal or gastrointestinal, is highly dynamic with respect to its physiology, which renders the vaginal environment an uncertainty factor with respect to retention of vaginal dosage for ms, absorption of drugs, their metabolism and their elimination from the vagina. Conventionally, vaginal delivery was restricted to locally acting drugs such as antibacterial, antifungal, anti-viral, spermicidal, labour-inducing agents, prostaglandins and steroids. Although with time, the potential for systemic delivery through vagina was explored because of its large surface area, high vascularity, and permeability to a wide range of compounds including peptides and proteins. It suggests a constructive substitute to oral and parenteral route. On the other hand, several drawbacks like cultural sensitivity, personal hygiene, gender specificity, local irritation need to be addressed during the design of a vaginal formulation. Presently available vaginal formulations have limitations, such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance. Attempts are being made to develop novel vaginal drug delivery systems that can meet the clinical as well as the user's requirements. This review will focus on the various aspects, scope and potential of vaginal drug delivery.

INTRODUCTION

Technologic progression in drug delivery has led to a wider choice of sites for drug administration. Conventionally, the routes mot commonly used were oral for systemic effects and topical for local effects. Medication can also be self-administered by inhalation, suppository, and in some cases injection. Other route of delivery were available but limited, because healthcare providers were required to administer them. Patients were also offered intranasal and transdermal formulations that could be self-administered. In the case of transdermal patches, patients were given an opportunity to administer several days' worth of therapy with a single application. These approaches represented an improvement over oral delivery because the hepatic first pass effect could be avoided. Today, there is growing interests in the vaginal route of administration, which also avoids the hepatic first-pass effect.

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The vagina allows woman to self administer medication continuously for weeks or months at a time with a single application that provide optimized pharmacokinetic profiles. These characteristic make the vagina an excellent route for drug administration.

The first vaginal applied formulations were used to treat local bacterial and fungal infections and inflammations. Today the high fungicidal vaginal infections which require often a systemically treatment are very problematically. An advantage would be an effective topical treatment. The development of novel products for female health, comprising therapeutic substances such as peptides, proteins, antigen, or antisense oligonucleotides, necessitates the design of high performance intravaginal drug delivery systems. In the case of local treatment it is challenging to design delivery systems providing high drug concentrations in the vagina for a prolong period of time, while in the case of systemic treatment; the major challenge is to gain high drug bioavailabity [1]. This route of administration offers advantages compared to other routes. Considerable advancement has been made in this research area over the past

few years and, at present, the anatomy and physiology, microflora and secretions of the vagina are well understood [2].

Presently available vaginal delivery systems have limitations, such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance.

However, despite all the advantage of a vaginal application, changes of the membrane during the menstrual cycle and postmenopausal must be taken into account. In postmenopausal woman the reduced epithelial thickness may change the original absorption rates of drugs significantly [3]. Many drug delivery systems are based on mucoadhesive polymers. Mucoadhesion is another version of the bioadhesion because the target is still the underlying tissue. These polymers are able to swell rapidly when placed in aqueous environment and therefore exhibiting a controlled drug release [4-10]. As a result, the therapeutic efficacy of locally acting drugs can be improved by their increased availability at the target membrane. Therefore, these macromolecules, such as poly (acrylates), cellulose derivatives, chitosan and many others, are very important excipient for future formulations.

Anatomy and Physiology of Vagina Related to Drug Delivery
The vagina plays a major role in reproduction and it is an important organ of the reproductive tract.

The wall structure
It is a strong canal of muscle and approx. 7.5 cm (centimeter) long that extends from the uterus to the vestibule of the external genitalia (Fig.1.).
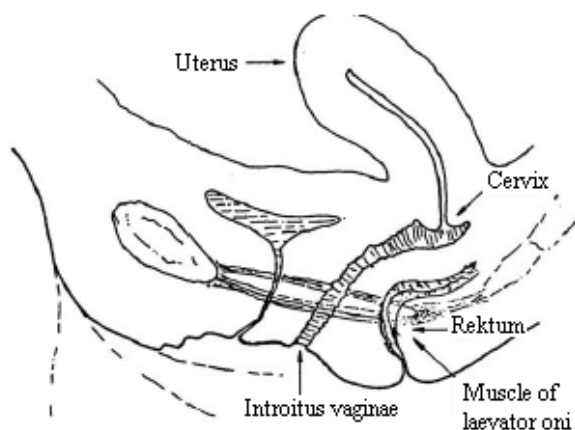

Figure1: Graphical description of the vagina. The vagina is located between rectum and bladder.

For enough elasticity the vaginal wall is crosswise fold (Fig.2.). The vagina is positioned between rectum, bladder and urethra [12]. The function and construction is significantly different to the intestinal wall. In contrast to the intestine there is no peristaltic motion but it is also not rigid. The vaginal wall consists of three layers: the epithelial layer, the muscular coat and tunica adventitia. A cell turnover of about 10–15 layers is estimated to be in the order of 7 days.
The epithelium is a noncornified, stratified squamous epithelium. The thickness is dependent on age. With hormonal activity the vaginal epithelium increases in thickness and is highest in the proliferative stage and reaches the highest glycogen content during ovulation. Although the cyclic changes of the vaginal epithelium are less pronounced than of the endometrium, although differential cytology of the vaginal epithelium can be used to identify the cycle stages. The epithelium thickness is also dependent on the different life stages like newborn, child, adult and menopause (Fig.3.).
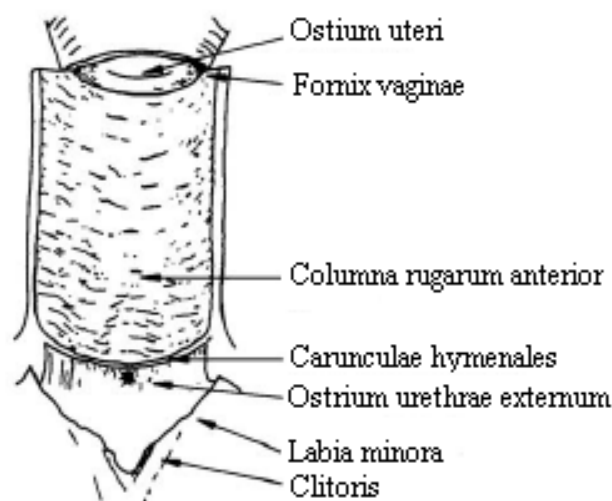

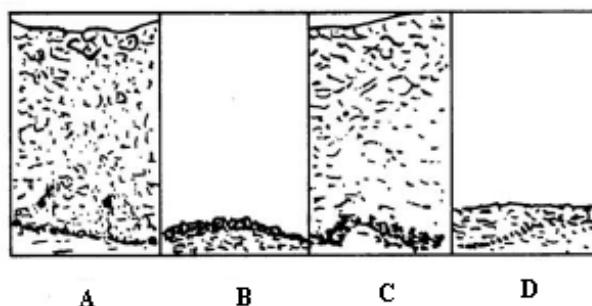**Figure 2:** Inside the upper vaginal wall.

Figure 3: Comparison of epithelial thickness of the vaginal tissue,
A-newborn, B-child, C-adult, D-menopause

Arteries and veins
The main blood supply to the vagina is through the vaginal branch of the uterine artery.

Epithelium
The vagina has unique features in terms of micro flora, pH and cyclic changes, and these factors must be considered during the development and evaluation of vaginal delivery systems. While the vaginal epithelium acts as a physical barrier (25 layers thick with estrogen present), cervical mucus, vaginal secretions, and local bacterial flora also help to protect the vagina against infection. The stratified squamous epithelium sheds constantly, making it difficult for organisms to invade or access the basement membrane/capillary bed [12].

Micro flora
The ecology of the vagina is influenced by factors such as the glycogen content of epithelial cells, glucose, pH, hormonal levels, and trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery.

The vaginal flora is a dynamic system mainly consisting of Lactobacillus (Do¨ derlein's bacilli) which is the most prevalent organism in the vaginal environment together with many other facultative and obligate aerobes and anaerobes. The glycogen content of superficial vaginal epithelium showed a tendency to increase throughout the cycle and then fall in the late premenstrual phase. This was according the estrogen excretion through the cycle [12]. As the estrogen production decreases during the pre-menopause and ongoing menopause there is a permanent decrease in the vaginal glycogen content. The acidophilic organisms are no longer dominating.

Vaginal pH
Normal micro flora predominantly lactobacilli produce sufficient lactic acid to acidify vaginal secretions to pH 3.5–4.5. This value is maintained by the lactobacilli which convert glycogen from exfoliated epithelial cells into lactic acid [13, 14]. The pH changes with age, stages of menstrual cycle, infections and sexual arousal. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase the pH [2, 15]. The pH plays also a role in amount of drug absorption and is important for drug delivery systems.

Cyclic changes
Changes in hormone levels (especially estrogen) during the menstrual cycle lead to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions [16]. The variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes further complicate the problem of achieving consistent drug delivery [17, 18].

Vagina as an Application Site for Drug Delivery
The anatomical position, the rich blood supply and the large surface area of the vagina predestines it as an application site for systemic drug delivery. In numerous studies a good permeability to a wide range of compounds including peptides and proteins [19-21] has been shown. The vaginal route offers a favorable alternative to the parenteral route for some drugs such as calcitonin [5], bromocriptine [22, 23], propranolol [24], oxytocin [25, 26] LHRH agonists [27], human growth hormone [28] and steroids used in hormone replacement therapy or for contraception [29]. Compared with the oral cavity, the vagina might serve as a better route for the delivery of hormonal contraceptives owing to the lack of drug interactions observed in the gastrointestinal tract. However, despite all these advantages, the vagina has not been extensively explored for systemic delivery because of gender specificity and cyclic variations.

Since now the vagina has been studied as a favorable site for the local delivery of drugs, specifically for female-related conditions. Traditionally, the vaginal cavity has been used for the delivery of locally acting drugs such as antibacterial, antifungal, antiprotozoal, antiviral, anti-inflammatory, and spermicidal agents, prostaglandins and steroids. The vaginal route also has potential for the uterine targeting of active agents such as progesterone and danazol [30-32]. The plasma concentrations of vaginally administered progesterone were found to be higher in the uterine artery than in the radial artery, indicating a preferential distribution of progesterone to the uterus. This confirmed the existence of direct local transport from the vagina to the uterus, termed the 'first uterine pass effect [33].

Advantages of vaginal drug delivery
Despite the fact that vaginal delivery is only available for females there are a number of

advantages for the vaginal route of administration like:

- Avoidance of hepatic first-pass metabolism is particularly advantageous for compounds that undergo a high degree of hepatic metabolism e.g. by the greater bioavailability of propranolol after vaginal administration compared with oral delivery[24]
- Reduction in the incidence and severity of gastrointestinal side effects, as observed during the vaginal delivery of bromocriptine[23]
- Reduction in hepatic side effects of steroids used in hormone replacement therapy or contraception [34, 35]
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by parenteral routes.
- Another advantage is the possible self-insertion and removal of the dosage form[36]

Lowering the incidence of side effects will increase the acceptability of a product and thus enhance patient compliance.

Limitation of vaginal drug delivery

In addition to being gender specific, the vaginal route is less preferable in terms of convenience depending on the dosage form. Another disadvantage is the influence of the estrogen concentration on the permeability of the vaginal membrane, which can influence the pharmacokinetics of drugs designed for systemic action [37, 38]. The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) [39] and this amount is decreasing with increasing age. This volume may also affect the vaginal absorption of drugs. As a drug must be in solution before it can be absorbed the presence of a film of moisture will be an advantage but in contrast to this the presence of thick cervical mucus may present also a barrier to drug absorption. Finally the pH of the fluid may affect the drug absorption too as it can be supposed that unionized forms will be preferable absorbed.

Factors Influencing Vaginal Absorption of Drugs

On one hand physiological factors like cyclic changes (under the influence of hormones such as oestrogen, progesterone, lutenising hormone, follicle stimulating hormone), thickness and porosity of the epithelium and volume, viscosity and pH of the vaginal fluid have a considerable influence on vaginal drug absorption. Vaginal epithelium has a lower enzyme activity compared to the GI tract. The variations in the enzyme activity with cyclic and hormonal changes affect vaginal drug delivery. And on the other hand physicochemical properties of drugs like solubility, dissolution rate, pKa, chemical structure, chemical stability, charge on the membrane surface, pore size molecular weight and lipophilicity the absorption across the vaginal epithelium. Improvement of vaginal absorption by using penetration enhancers e.g. PEG (poly ethylene glycol), by increasing the contact time between the dosage form and the vaginal membrane, by using mucoadhesive polymers e.g. Carbopol, by increasing vaginal blood flow, thereby raising the concentration gradient across the vaginal mucosa and by the use of pro-drugs enhances drug permeability through modification of the hydrophilicity or lipophilicity of the drug. The extent of flow and retention of the medicament within the vaginal cavity depends on the type of formulation. Lower vaginal residence time can be improved by a bioadhesive dosage form that results in prolonged contact with the absorbing surface, and hence, better drug absorption. Drugs are transported across the vaginal membrane by the transcellular route, intracellular route or vesicular and receptor-mediated transport mechanisms [15]. A physical model of the vaginal membrane as a transport barrier has been described [40].

Types of Vaginal Drug Delivery Systems

In development of vaginal dosage form, the following consideration should be addressed [2].

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

In addition offensive odors, staining, tissue irritation or pain during sexual intercourse are undesirable.

Novel Concepts in Vaginal Drug Delivery

Genital infections are commonly treated with imidazole derivative antifungal agents, since they are locally active with no major side effects. Current vaginal delivery systems include creams, foams, gels, tablets, pessaries and irrigations. The efficacy of these preparations is however limited due to their short residence time in the genitourinary tract. They are removed rather

rapidly by the self-cleansing action of the vaginal tract. Moreover, the physiological conditions of the genital tract limit long residence times and impair the therapeutic efficacy of the immediate-release drug requiring multiple and frequent administration for treatment. It is believed that vaginal therapy can be significantly improved if a delivery system can retain the drug at the site of administration for a prolonged period compared to conventional dosage forms. Approaches used for the development of Vaginal Drug Delivery Systems include novel drug loaded inserts which are on the market, hydrogel systems containing phase change polymers such as poloxamer 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 are existing, mucoadhesive drug delivery systems (These polymers are able to swell rapidly when placed in aqueous environment and therefore exhibiting a controlled drug release) [10]. The composition of vaginal dosage forms will be the focus of interest in the future novel forms are liposome's, micro emulsion based vaginal gel, vaginal rings [41,42], cubic gels [43], formulations based on polystyrene [44] and formulations based on silicone elastomers [45]. One interesting group of auxiliary agents is the mucoadhesive polymers, which are basis of new designed systems [46, 47].

Novel intravaginal drug delivery system includes those that employ bioadhesive materials. Mucoadhesive hydrogels are weakly- crosslinked polymer able to swell in contact with water and to spread on to a surface of mucus. Thus their bioadhesive properties may provide controlled drug delivery system with a prolong residence and intimate contact in vagina. Many hydrophilic polymers and hydrogels have been used in vaginal products. Bioadhesion is thought to involve an initial interaction of hydrogel with the mucosal surface, which requires matching polarity between the tissue surface and polymer surface, and subsequently, an interpenetration of mucosal surface, by the polymer chains of hydrogel. Replens®, which has been marketed as a bioadhesive moisturizer and which remains in vagina for 2-3 days, consist of a bioadhesive cross-linked polycarbophil.

The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems, to retain systems for treating largely local (although some systemic) conditions, or for use in contraception [48]. Gels are one of the most commonly studied mucoadhesive formulations for vaginal drug delivery [49].

CONCLUSION

The safety and efficacy of vaginal administration have been well established through its long and well-studied history. Drugs are easily and rapidly absorbed through the vaginal epithelium into the systemic circulation, and there is no adipose tissue or other cell layers with metabolic enzymes to traverse as with the transdermal or oral routes. The GI tract and hepatic first-pass effect are avoided. Vaginal administration allows nondaily, low, continuous dosing, in turn, achieve a lower incidence of side effects and improve patient compliance. 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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