The scope and potential of vaginal drug delivery

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The vagina, in addition to being a genital organ with functions related to conception, serves as a potential route for drug administration. Mainly used for local action in the cervico-vaginal region, it has the potential of delivering drugs for systemic effects and uterine targeting. Currently available vaginal dosage forms have several limitations, necessitating the need to develop novel drug delivery systems. In addition, consideration of the regulatory aspects and consumer preferences for vaginal formulations is also required in the early stages of development.

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▼The vagina, as a site for drug delivery, offers certain unique features that can be exploited in order to achieve desirable therapeutic effects. Considerable progress 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. By contrast, the scientific knowledge regarding the possibilities of drug delivery via the vagina is limited. To date, there are only a limited number of vaginal dosage forms (VDFs) available, although various possibilities are presently being explored.

The currently available VDFs 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 (NVDDS) 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.

Vaginal anatomy and physiology with reference to drug delivery

The vagina is an important organ of the reproductive tract with a major role in reproduction[1,2]; it has unique features in terms of secretion pH and microflora, and these factors must be considered during the development and evaluation of VDFs.

Vaginal secretions

The vaginal epithelium is usually considered to be a mucosal surface, although it has no goblet cells and lacks the direct release of mucin. Vaginal discharge is a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, secretions of the Bartholin's and Skene's glands, leukocytes, endometrial and tubal fluids[3,4]. The cervical mucus contains inorganic and organic salts, mucins, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). Estrogens and sexual stimulation increase vaginal fluid secretion.

Vaginal pH

The vaginal pH of healthy women of reproductive age is acidic (pH = 4–5); this value is maintained by lactobacilli that convert glycogen from exfoliated epithelial cells into lactic acid. 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 pH (Ref. 5).

Microflora

The vaginal flora is a dynamic and closely interrelated system[1]. The ecology of the vagina is influenced by factors such as the glycogen content of epithelial cells, glucose, pH, hormonal levels, trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. Lactobacillus (Döderlein's bacilli) is the most prevalent organism in the vaginal environment together with many other facultative and obligate aerobes and anaerobes.

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Table 1. List of vaginal preparations recently developed or under development

Preparation	Active ingredient	Company	Status
Acidform (gel)	–	TOPCAD (IL, USA)	Phase I/II clinical trials
Advantage-S (gel)	Nonoxynol-9	Columbia Laboratories (FL, USA)	Market
BufferGel™ (gel)	–	ReProtect (MD, USA)	Phase I clinical trials
CCVR (Combined contraceptive vaginal ring)	3-Ketodesogestrel ethinylestradiol	Organon (NJ, USA)	Phase III clinical trials
Cleocin (cream)	Clindamycin phosphate	Pharmacia & Upjohn (MI, USA)	Approved (USA)
Crinone® (gel)	Progesterone	Wyeth–Ayerst Laboratories (PA, USA)	Approved (1997)
Efamast	Evening primrose oil	Scotia Holdings (Surrey, UK)	Phase II clinical trials (Europe)
Estradiol	17-β-estradiol	Watson Pharmaceuticals (CA, USA)	Phase II/III trials (USA)
Estring Vaginal Ring	Estrogen	Pharmacia & Upjohn (MI, USA)	Approved (1998)
Femstat one (Emulsion)	Butoconazole	Hoffmann–LaRoche Laboratories (NJ, USA)	Approved (USA)
Gynol II jelly	Nonoxynol-9	Ortho Pharmaceuticals (NJ, USA)	Market
Invisible condom	Thermoreversible gel	Laval University (Canada)	Phase I clinical trials
LASR Suppository	Nonoxynol-9	Advanced Care Products (NJ, USA)	Phase II clinical trials
Pro 2000 (gel)	Napthalene 2-sulfonate	Procept (MA, USA)	Phase II NIAID trial
Replens® (gel)	–	Columbia Laboratories (FL, USA)	Market
Savvy™ (gel)	Glyminox	Biosyn (PA, USA)	Phase I clinical trials

Cyclic changes

The 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[6]. The variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes further complicate the problem of achieving consistent drug delivery[5].

Vagina as a site for drug delivery

The vagina has been studied as a favorable site for the local and systemic 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, labor-inducing and spermicidal agents, prostaglandins and steroids[7]. In the past decade, major advancements have been reported in the field of 'microbicides', that is, compounds or formulations that can prevent the transmission of sexually transmitted diseases (STDs), including AIDS. To date, there are ~60 microbicides in different stages of development[8]. Microbicides can provide better protection than standard prevention tools (e.g. condoms and behavioral modifications). These are controlled by the user, can meet reproductive health requirements, offer 'bidirectional' protection (i.e. protection to both partners) and provide greater control over the risk of exposure to STDs. A vaginal wash can be used by HIV-positive women during childbirth as a low cost way to reduce the risk of perinatal transmission[9] (http://www.thebody.com/bp/mar00/mar00ix.html).

The vagina also has great potential for systemic delivery because of its large surface area, rich blood supply and permeability to a wide range of compounds including peptides and proteins[10]. It offers a favorable alternative to the parenteral route for some drugs such as bromocriptine[11], propranolol[12], oxytocin, calcitonin, LHRH agonists, human growth hormone, insulin and steroids used in hormone replacement therapy or for contraception[5]. 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.

The vaginal route also has potential for the uterine targeting of active agents such as progesterone and danazol[13,14]. 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'[13].

Some of the vaginal products recently introduced into the market and in various stages of development are listed in Table 1.

Advantages

The advantages of the vaginal route of administration are:

- The avoidance of hepatic first-pass metabolism – this has been reflected by the greater bioavailability of propranolol

after vaginal administration compared with oral delivery[12].
- A reduction in the incidence and severity of gastrointestinal side effects, as observed during the vaginal delivery of bromocriptine[11].
- A reduction in hepatic side effects of steroids used in hormone replacement therapy or contraception[15].
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by other parenteral routes.
- The self-insertion and removal of the dosage form is possible[7].

Limitations

In addition to being gender specific, the vaginal route is less preferable in terms of convenience. The permeability of the vagina is strongly influenced by the estrogen concentration, which can influence the pharmacokinetics of drugs designed for systemic action[7].

Dosage forms

Creams, gels, tablets, capsules, pessaries, foams, ointments, films, tampons, vaginal rings and douches are the most commonly used VDFs[16,17]. Vaginal formulations are also used in traditional medicine systems, for example, V-gel (Himalaya Drugs Company, India), which is an ayurvedic vaginal formulation for the treatment of candidiasis, trichomoniasis, bacterial and senile vaginitis. In addition, polyherbal microbicides are under development[18]. Intravaginal systems are also available for controlled drug delivery in animals[19].

Vaginal absorption of drugs

Drugs are transported across the vaginal membrane by the transcellular route, intracellular route or vesicular and receptor-mediated transport mechanisms[5]. A physical model of the vaginal membrane as a transport barrier has been described[20,21]. The physiological factors (e.g. cyclic changes in the thickness and porosity of the epithelium, volume, viscosity and pH of the vaginal fluid) and physicochemical properties of drugs (e.g. molecular weight, lipophilicity and ionization) affect absorption across the vaginal epithelium[5]. The absorption of drugs, targeted for local action in the vagina, is not desirable.

Novel concepts in vaginal drug delivery

Several aesthetic and functional qualities must be incorporated into VDFs. NVDDS need to be designed with desirable distribution, bioadhesion, retention and release characteristics. The conventional VDFs, such as suppositories, gels, creams and foams can meet some but not all of these requirements. These features can be achieved by the use of bioadhesive[22] and other novel delivery systems[23–26].

Bioadhesive delivery systems

Bioadhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate have been developed and studied recently. In a study on postmenopausal women, a bioadhesive formulation, Replens gel (1–3% polycarbophil gel), was shown to be retained in the vaginal cavity for 3–4 days[22]. However, conflicting reports were obtained when the same formulation was studied for retention in the human vagina[27]. There was a lack of significant retention of the gel in five out of the six volunteers studied. Another polycarbophil-based bioadhesive vaginal gel, Crinone®, provided a prolonged release of progesterone in postmenopausal women[28].

An acid buffering gel, Acidform, was found to form a thin bioadhesive layer over the genital tract surface in Phase I clinical studies[29,30]. Some bioadhesive formulations have been found to reduce the conventional treatment time of fungal infections by at least 25% (Refs 31,32). For systemic delivery, insulin suspended in a polyacrylic acid gel base was observed to facilitate the rate of vaginal absorption in alloxan diabetic rats and rabbits[33].

In addition to semi-solids, polycarbophil-based bioadhesive tablets of metronidazole were tested for adhesion on bovine vaginal tissue[34]. In another study, metronidazole tablets in a modified starch–polyacrylic acid mixture showed an increased potential for curing bacterial vaginosis[35].

A bioadhesive formulation might not necessarily contain a therapeutic agent and can be used as a moisturizer for the treatment of dry vagina[36]. Several bioadhesive polymers have been reported for different mucosal sites such as the buccal cavity, stomach and intestine[37]. In most of the vaginal preparations, either carbopol or polycarbophil has been used as the bioadhesive polymer[22,28,34]. The necessary assemblies have been designed to measure the bioadhesion characteristics of polymers and formulations in a simulated vaginal environment[38], and these have been used to select the appropriate polymers in terms of bioadhesion in a vaginal environment.

Other novel delivery systems

Phase change polymers such as poloxamers exhibit sol–gel transition in response to body temperature, pH and specific ions[23], and they prolong the residence time of the dosage form in the vagina. However, these can interfere with sexual intercourse.

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[26,39]. Non-aqueous solutions of the copolymer in hydrophilic excipients undergo *in situ* gelation in a short period of time after application. These *in situ* gelling liquid formulations can provide: (1) the necessary

vaginal and cervical coverage as a result of their fluidity before gelation, and (2) retention owing to the formation of a mucoadhesive gel. Although studied to a limited extent, liposomes also have the potential to provide the controlled release of a drug after vaginal administration[24,25].

Consumer preferences

Vaginal products need to be designed for women's convenience. In recent years, the need to acquire knowledge of women's interests and preferences for a vaginal product has been recognized in order to ensure product acceptability. The information from various surveys suggests that a vaginal formulation must possess the following characteristics[40–45]:

- no adverse effect on coitus;
- odourless and colourless;
- can be applied several hours before intercourse;
- no leakage, messiness or feeling of fullness;
- no irritation, itching, burning or swelling; and
- convenient to insert and/or apply with or without an applicator.

The user's perspectives and their choice of formulation vary depending on the individual, partner(s), cultural norms, age, economical, social and climatic conditions of the specific geographical region. The popularity of VDFs can be different among women from different backgrounds and countries. For example, tablets are the most popular dosage form in the Indian subcontinent for climatic and cost reasons. Gels are the most preferred formulation in New York (USA), and film formulations are preferred in countries such as Zimbabwe, Thailand and Cote d'Ivoire[42]. There is an urgent need to collect this kind of data for other countries.

Some women prefer a product that can be used without their partner's knowledge, particularly in the case of a non-cooperative partner. By contrast, there are women who take into consideration their partner's perceptions of product characteristics. In future studies, it is therefore critical that men's attitudes and beliefs regarding the use of vaginal preparations are explored[42]. It was shown that men in Zimbabwe prefer the use of microbicides with proven safety and efficacy, rather than condoms[46].

In vitro and *in vivo* evaluation of vaginal formulations

A vaginal formulation must be evaluated by both *in vitro* and *in vivo* experimentation for various functional requirements. *In vitro* studies include the determination of release and bioadhesive characteristics in addition to various physical and chemical properties of formulations. The release characteristics of a drug from a vaginal formulation can be determined by membrane diffusion studies, microbiological methods[47] and a vaginal dissolution tester[48]. Disintegration or dissolution tests, uniformity of content or weight are some of the official tests for pessaries[49]. The bioadhesive strength has been estimated with the help of assemblies based on the principle of measuring tensile strength or shear stress required to separate the formulation from the vaginal mucosa[34,50].

In vivo studies are carried out for the assessment of efficacy, distribution, spreading and retention of formulations in the vagina. The rate and extent of drug release can be determined by: (1) monitoring quantities of systemically absorbed materials, for example, peptides and proteins[51], (2) measuring the pharmacological activity[33,52], and (3) analysis of vaginal lavage[53]. Gamma scintigraphy is a valuable method for assessing the distribution, spreading and retention of vaginal formulations in sheep and human females[27,54]. Colposcopy has also been used for direct *in vivo* visualization and analysis[55].

In the process of the development of a vaginal formulation, various animal models such as sheep, rat, rabbit, rhesus monkey, macaque monkey, dog and mice have been used[5]. The rabbit is the recommended model for vaginal irritation studies. There is significant species variability in the anatomy and physiology of the vagina of different animals. Because of interspecies differences, the evaluation of vaginal formulations in human subjects is desirable.

Simulated vaginal fluid

To simulate the vaginal environment, different compositions of vaginal fluid have been used for *in vitro* testing of vaginal formulations[38,56,57]. A chemically defined medium that simulates female genital tract secretions that can support the growth of vaginal microflora has also been reported[58].

General regulatory requirements

There is a lack of well-defined guidelines and regulations for vaginal products in most countries. The official compendia have little information on quality control and other aspects of such products. A review of the FDA regulatory requirements is necessary before the development of vaginal formulations (http://www.fda.gov/cder/guidance/index.htm). The FDA has issued guidelines on the development of vaginal contraceptives and antimicrobial drugs used in the treatment of gonorrhoea, bacterial vaginosis and vulvo-vaginal candidiasis. According to the FDA, nonclinical, pharmacological and toxicological requirements must be submitted as supportive evidence along with an Investigational New Drug Application (NDA). Segment I (fertility and reproductive performance), II (teratology) and III (perinatal and postnatal) reproduction studies are required before Phase I, Phase II/III trials and NDA submission, respectively.

Conclusions

The vaginal route has been traditionally used for the local application of drugs, but is now gaining importance as a possible site for systemic delivery. For the prevention of STDs, AIDS and conception, the use of vaginal products might provide a better alternative to behavioral modifications and the use of condoms. Novel developments such as bioadhesive systems and liposomes overcome some of the major limitations of conventional vaginal products. The consideration of women's opinions on vaginal products is also important for the development of acceptable dosage forms and better compliance. Extensive research is required for a reasonable understanding of various aspects of vaginal drug delivery and rational development of user-friendly formulations.

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