

Vaginal drug delivery systems: A Review of Current StatusN. DOBARIA^{1*}, R. MASHRU¹ AND N. H. VADIA²

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Among the various routes of drug delivery, the vaginal route offers many advantages due to its large permeation area, rich vascularization, avoidance of first pass metabolism and relatively low enzymatic activity. Several studies have shown that the vaginal cavity is an effective route for drug administration intended mainly for local action. In addition, it has the potential of delivering drugs for systemic effects and uterine targeting. Use of the vaginal mucosa for drug absorption was first attempted by Sobrero and since then much research has been done on the administration of drugs through this route. In recent years, the level of interest in the design and application of different dosage forms for vaginal use has increased considerably. Vaginal drug delivery specifically refers to the delivery of drugs within or through the vaginal mucosa for local or systemic pharmacological action. The rate and extent of drug absorption after intravaginal administration may vary depending on vaginal physiology, age of the patient, stage in the menstrual cycle, pathological conditions and formulation factors. This review highlights the benefits and limitations of vaginal drug delivery, methodology in evaluation of vaginal drug delivery systems, pharmaceutical aspects and gives a summary of recent advances made in the field of vaginal drug delivery. The various dosage forms in different stages of development and in the market are also reviewed.

Key words: Vaginal delivery, microbicide delivery, solubility modifier, bioadhesion; formulation design.

INTRODUCTION

The vaginal cavity is an important area of the reproductive tract and acts as a favorable site for drug administration due to avoidance of first pass effect, large permeation area, rich vascularization and relatively low enzymatic activity [1]. In recent years, research has been focused on vaginal drug delivery systems as logical alternatives to oral or parenteral drug administration. Many studies have demonstrated the superiority of vaginal over oral drug administration in terms of minimizing general and gastrointestinal side effects. The search for non-invasive drug delivery systems continues due to poor patient compliance and acceptance, limited market size and drug uses, coupled with the high cost of disease

management. The vaginal cavity has a potential for noninvasive, controlled transmucosal delivery of both local and systemic therapeutically active compounds [2]. The vagina has a great potential for systemic delivery of a wide range of compounds including proteins and peptides [3]. Formulation and delivery of microbicides is being developed as a new therapeutic approach to prevent HIV and other sexually transmitted diseases (STDs). The vaginal cavity is also an effective site for the uterine targeting of various therapeutic agents such as terbutaline, progesterone and danazol [4]. Recently, the vagina has been studied as a novel route for the delivery of chemotherapeutic agents for treatment of all cancers [5]. Creams, tablets, gels, suppositories, foams, ointments, tampons

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and inserts are commonly used as vaginal drug delivery systems. The currently available vaginal dosage forms have certain limitations such as messiness, leakage and low residence time, leading to poor patient compliance and loss of therapeutic efficacy. Therefore, novel concepts and dosage forms are needed. Extensive research is ongoing to develop better vaginal drug delivery systems that can fulfill the user's requirements. Some of the vaginal products recently introduced into the market and in various stage of development are listed in Table 1. This review highlights several recent advances in vaginal drug delivery.

BENEFITS OF VAGINAL DRUG ADMINISTRATION

In the vagina, arteries and veins form a dense network which provides a rich blood supply and consequently the vagina is well suited for the rapid and steady uptake of hormones [6]. Drugs administered via the vagina are not subject to the first-pass effect and gastrointestinal interferences with absorption of medication are avoided. This has been demonstrated by the greater bioavailability of misoprostol following vaginal as opposed to oral administration [7]. Vaginal administration often minimizes side effects associated with the oral route. An example is the administration of bromocriptine vaginally in treatment of hyperprolactinemia in women who suffer from nausea and vomiting following oral administration [8].

Bioadhesive vaginal delivery systems have several advantages when compared to conventional dosage forms. Firstly, the bioadhesive vaginal formulations are readily localized in the region of application thus improving the bioavailability of drugs. Greater bioavailability of insulin [9], calcitonin [10], progesterone [11] and estrogen [12] was observed from bioadhesive vaginal formulations. Secondly, these delivery systems provide intimate contact of the formulation with the underlying absorption surface. This allows for modification of tissue permeability for absorption of macromolecules such as proteins

and peptides [3]. Thirdly, it permits continuous and prolonged residence of the dosage form at the site of application. Lastly, it reduces side effects due to avoidance of repeated administration of the drug.

VAGINAL ANATOMY AND PHYSIOLOGY WITH RESPECT TO DRUG DELIVERY

The vagina is a fibromuscular 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 [13]. The vaginal rugae and microridges 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 [14]. The vagina has remarkable features in terms of vaginal secretion, pH, enzyme activity and microflora. 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 [15]. 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 \geq human \geq rat [16]. The human genital tract has lower enzymatic activity leading to less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract [3].

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 [17].

Table 1. List of Vaginal Preparations Recently Developed or Under Development

Product name/ Dosage Form	Active Ingredient	Manufacturer or Developed by	Status
Prochieve™ 4% (Bio-adhesive gel)	Progesterone	Columbia laboratory	Market (USA)
Advantage- S	Nonoxynol-9	Columbia laboratory	Market (USA)
Chronodyne™ (Bio-adhesive gel)	Terbutaline	Ardana bioscience Ltd	Phase II clinical trial
Lidocaine	Lidocaine	Columbia laboratory	Phase III clinical trial
Testosterone (gel)	Testosterone	Columbia laboratory	Phase III clinical trial
Prepidil (cervical gel)	Dinoprostone	Pharmacia & Upjohn Company	Market
Culturelle VC (capsule)	Probiotics	Pharma Dyanemics (Pvt.) Ltd.	Market
Pro 2000 (gel)	Naphthalene2- sulfonate	Indevus Pharmaceuticals, Inc.	Phase III clinical trial
Vagifem® (tablet)	Estrogen	Novo Nordisk	Market
Crinone	Progesterone	Wyeth-Ayerst laboratories	Approved (1997)
Gynazole-1	Butoconazole nitrate 2%	KV Pharmaceuticals, USA.	Market
Clindesse	Clindamycin phosphate	KV Pharmaceuticals, USA.	Market
Gyno-V	Neomycin Sulfate Polymyxin B Sulfate Nystatin	Unimed Pharm, Inc.	Market
Camazole (Tablet)	Clotrimazole	Keun Wha Pharmaceutical Ltd.	Phase II/III clinical trial
Emmelle (gel)	Dextrin sulphate	M - L Laboratory	Phase III clinical trial
Cervidil (Insert)	Dinoprostone	Forest Pharmaceutical Inc.	Market
Savvy™	Glyminox	Biosyn	Phase III clinical trial
Vaginal contraceptive Film	Nonoxynol-9	Apothecus Pharmaceutical	Market
Estring (Vaginal ring)	Estrogen	Pharmacia & Upjohn Company	Approved (1998)
Gynol II (Jelly)	Nonoxynol -9	Ortho -McNeil	Market
KY Plus (Jelly)		Johnson & Johnson	Market
Ovule	Miconazole nitrate	Personal Care Products, NJ	Phase IV
Protectaid (Sponge)	Nonoxynol- 9 Benzalkonium chloride	Axcan Pharma	Market
Invisible condom	Sodium lauryl sulphate	Laval university	Phase I/II clinical trial
Viread (gel)	Tenofovir	Gilead Science	Phase II clinical trial
Ushercell (gel)	Cellulose sulphate	Polydex Pharmaceuticals	Phase III clinical trial
Carraguard (gel)	Carrageenan/ PC-515	Population Council	Phase III clinical trial
Placebo gel	Hydroxy ethyl cellulose	Biosyn	Phase I clinical trial
Vaginal gel	Cellulose sulphate	Family healthcare	Phase III clinical trial

The pH changes with age, stage in the menstrual cycle, infections, estrogen levels and variations in the levels of cervical mucus. The control of vaginal pH is a critical factor for successful vaginal delivery of drugs [18].

The change in hormone levels with age, during intercourse and various phases of the menstrual cycle leads to alteration in vaginal secretion, pH, enzyme activity as well as changes in the thickness and permeability of the epithelium all of which complicate the problem of achieving consistent drug delivery. [19].

VAGINAL ROUTES OF DRUG ABSORPTION

The drug is delivered in the vagina mainly via two routes: intravaginally to the vaginal epithelium or transvaginally through the vaginal mucosa to uterus and systemic circulation [20]. Cicinelli *et al.* reported that the vagina has specific blood flow characteristics, either by a portal type circulation or by venous and lymphatic channels, that allow bypassing the gastrointestinal tract absorption and liver detoxification and permit preferential transport of drug molecules from the vagina to the uterus and systemic circulation [21]. Several physical models have been devised to study the vaginal permeability of drugs [22]. Many therapeutic compounds have been shown to be absorbed through the vaginal mucosa [23-29]. Antifungal agents such as tioconazole, clotrimazole and miconazole are topically administered to treat vaginal yeast infections [20-30]. On the basis of our knowledge of anatomical and physiological features of the vagina, it is likely that many other drugs will be formulated for vaginal administration in the future.

THE VAGINA AS A SITE FOR MICROBICIDE DELIVERY

Significant progress has been reported in the area of vaginal microbicides. There are currently more than 50 potentially microbicidal products under development globally, of which 16 are in Phases I-III clinical trials. Recently, the vagina has been rediscovered as potential

route for microbicide and contraceptive delivery. Acidform[®] is a gel formulation that helps to maintain a low vaginal pH, immobilizes sperm and prevents multiplication as well as survival of STD causing organisms [31-32]. Cellulose acetate phthalate based sponges and those made from other cellulose derivatives are soft, mechanically resilient and thus ideally suitable as bio-erodible microbicidal vaginal devices [33]. Conceival is a novel non-toxic, nonspermicidal, self-emulsifying lipophilic gel with improved solubility of lipophilic anti-HIV microbicides [34]. Another vaginal product under development is a liposome preparation containing monoclonal antibodies that will completely agglutinate sperm in the ejaculate.

PHARMACEUTICAL ASPECTS

There are many pharmaceutical companies currently focusing on the development of novel vaginal drug delivery systems for contraception, treatment of vaginal infections, STDs and other gynaecological conditions. These innovative delivery systems may lead to extended product shelf life making the products competitive in the market place. The alternative approach of research based pharmaceutical companies would be to develop formulations or new dosage forms using novel excipients that offer distinct advantages over conventional drug delivery systems. In order to achieve desirable drug characteristics different approaches are used [35]. The compatibility between the drug and excipient can easily be evaluated by thermal (Differential Scanning Calorimetry) and isothermal (HPLC) stress testing [36].

Penetration Enhancers: Penetration enhancers are capable of promoting absorption and penetration of drug through the vaginal mucosa by decreasing the penetration barrier [9, 37]. Currently, the most preferred penetration enhancers include non-ionic surface active agents, bile salts, benzalkonium chloride, hyaluronic acid [38], polyethylene glycol, ethoxydiglycol and interesterified stone oil [5, 20].

Solubility Modifiers: The poor solubility of drugs in simulated vaginal fluid may affect the release pattern of a drug from its device, which influences the onset and therapeutic efficacy of the drug. Water-soluble drugs are good candidates for vaginal drug delivery. The aqueous solubility of a drug can be increased by several mechanisms such as addition of solubilizing agents and cosolvency [39]. The most commonly used solubilizing agents include citric acid, ethylenediamine-tetraacetate, sodium meta-phosphate, polyvinylpyrrolidone, sorbitan, tween 80, polyoxyethylene, polyoxyethylene n-alkyl ethers, poloxamers, and cyclodextrin [40]. For example, a novel itraconazole formulation intended for vaginal use is based on hydroxypropyl- β -cyclodextrin, a functional excipient that increases drug solubility [41].

Mucoadhesive agents: Mucoadhesive agents permit a close contact of formulation with the vaginal mucosal surface by promoting adherence [42]. These include polycarbophil, hyaluronic acid, chitosan, sodium alginate, tragacanth, carbomer, acacia, sodium carboxymethyl cellulose or other cellulose derivatives, Carbopol 974P-NF, Carbopol 971P-NF and other copolymers of acrylic acid [43]. Some of these polymers may possess site-specific bioadhesive properties. For example, xanthan gum and sodium alginate show site-specific bioadhesive properties in a simulated vaginal environment [44]. Polycarbophil 934P exhibited pH-dependent bioadhesive properties [45].

RECENT ADVANCES IN VAGINAL DRUG DELIVERY

An important part of the product development strategy in the area of female healthcare is to develop a broad line of products designed for the unmet medical needs of women. The vast majority of presently available conventional formulations possess poor bioadhesive properties. They exhibit limited effectiveness due to rapid, uncontrolled release of the active

agents [46]. Conventional dosage forms frequently produce leakages and drip. There is a need for the development of innovative vaginal formulation technology that fulfills certain criteria such as desirable product dispersion throughout the vagina, retention for intended intervals, adequate release of drug and improvement of human reproductive health. These features can be achieved by the use of bioadhesive delivery system [42, 47] and other novel delivery systems [48]. The recent advances made in the vaginal drug delivery systems are summarized in Table 2.

Bioadhesive Delivery System

In bioadhesive delivery system, bioadhesive molecules capable of delivering the active compound for an extended period at a predictable rate are incorporated into a formulation [63]. The vagina is a highly suitable site for bioadhesive formulations. As a progressive hydration approach to bioadhesive delivery, the product absorbs moisture, becomes a gel and releases medication in a time-controlled manner. Equipment has been designed to measure the bioadhesion characteristics of polymers and formulations in a simulated vaginal environment [45].

Dry formulations achieve bioadhesion via dehydration of the local mucosa. Tablets that are placed directly between the vaginal mucosal surfaces have been demonstrated to be excellent bioadhesive formulations. For example, chitosan and sodium alginate based bioadhesive tablets were found to release 100 % of metronidazole over a period of 8 h in a buffer at pH 4.8 [64]. In another study, bioadhesive microparticles have also been investigated for the vaginal delivery of salmon calcitonin using HYAFF as bioadhesive polymer where microspheres showed increased bioavailability of drug. Water dispersible films are being used to deliver drugs directly to mucosal surfaces to form close contact with mucosal membrane [65].

Table 2. Summary of Recent Advances in Vaginal Drug Delivery

Drug	Formulation	Polymers	Result/Purpose of investigation	Ref
Insulin	Microsphere	HYAFF	Increased absorption from HYAFF microsphere compared to aqueous solution of the drugs	[9]
Salmon calcitonin	Microsphere	HYAFF	Same as above	[10]
Cellulose acetate phthalate	Sponge disc	HPMC/MC Pectin	A biodegradable microbicial vaginal barrier device for the prevention of STDs	[33]
Danazol	T- shaped preparation IUD- ring preparation Paste/ Spherical gel	Hyaluronic Acid or Modified hyaluronic	Novel pharmaceutical preparation for the treatment of gynaecological diseases	[49]
Acriflavine	Microsphere	MC/Carbopol 974 Sodium CMC/Alginate	Controlled release	[50]
Leuprorelin acetate	Intrauterine Device	Copolymer of lactic acid and glycolic acid polymer of lactic acid	Prolonged release of Leuprorelin acetate	[51]
Metronidazole	Tablet (Bioadhesive)	Chitosan, Sodium Alginate	Mucoadhesive dosage form	[52]
Benzylamine hydrochloride	Vaginal gel	Polyoxyalkylene block copolymer	Release of the active agent over an extended period of time (12 to 36 h)	[53]
Clotrimazole	Liposome gels (Bioadhesive)	Carbopol 974P	Novel delivery system for local therapy of vaginal infection	[54]
Clotrimazole	Tablet (Bioadhesive)	Chitosan-TGA conjugates	Significantly improved water uptake and cohesive properties of vaginal tablets	[55]
Chloramphenicol	Liposome gels (Bioadhesive)	Carbopol 974P	Sustained release of drug and novel delivery system for local treatment of bacterial vaginosis.	[56]
Clotrimazole	Pessaries	Polycarbophyl, HPMC Hyaluronic sodium salt	Good adhesion properties and capacity to hold the dosage form in the target site.	[57]
Oxybutynin	Vaginal ring	Trifluoropropylmethyl/ Dimethylsiloxane Polydimethylsiloxane	Controlable release of drug up to several days on single application	[58]
Acyclovir	Liposomal hydrogel (Bioadhesive)	Carbopol 974P	Sustained release and improved bioavailability	[59]
Progesterone	Vaginal ring	Polydimethylsiloxane	Advanced delivery system of hormone replacement in females	[60]
Ethinyl estradiol Etonogestrel	Vaginal ring	Ethylene-vinyl acetate copolymer	Reliable release of ≥ 2 active substances in a constant ratio over a prolonged period	[61]
Physiologically active peptides	Gel, tablet, film, soft capsule	Sucrose fatty acid ester organic acid	Excellent absorbability of the active ingredient	[62]

Ref = Reference, HPMC = Hydroxypropylmethyl cellulose, MHPC = Methylhydroxypropyl cellulose, PEG = Polyethylene glycol, CMC = Carboxymethyl cellulose.

Controlled release drug delivery systems can be achieved by the addition of time-release additives. Bioadhesive formulations based on carbomers and polycarbophil give satisfactory drug delivery within the vaginal cavity following the application of a single dose. For example, ProchieveTM is a bioadhesive gel used in hormone replacement therapy. Replens[®] is a mucoadhesive gel based on polycarbophil designed to be retained in the genital cavity for 3-4 days [45]. Francois *et al.* reported a mucoadhesive, cyclodextrin-based vaginal cream formulation of itraconazole which was found to be effective in the treatment vaginal candidiasis [41].

Other Novel Delivery Systems

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, polybutylmethacrylate, plasticized polyvinylchloride, plasticized nylon, plasticized polyethylene-terephthalate, polyethylene, polyacrylonitrile, polytrifluorochloroethylene, poly-4,4'-isopropylendiphenylene 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 antifertility effect over a prolonged period [66].

The timely gelation and retention of *in situ*-gelling vaginal formulations could be fundamental in improving the efficacy of drugs. The phase changes polymers composed of polyoxypropylene and polyoxyethylene are used to form thermoreversible gels when incorporated into aqueous solutions [67]. In addition, Poly (N-isopropylamide), Poloxamer 407[®] and Smart-Gel[®] polymers exhibit sol-gel transition in response to body temperature, pH and specific ions, therefore allowing

advantageous topical applications [68]. Chang *et al.* have recently reported a mucoadhesive thermosensitive gel that exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation [69].

Microemulsion based formulations that offer rapid dispersion and enhanced drug absorption profiles can be exploited for the development of novel vaginal delivery system [70]. GM-144, a novel lipophilic gel-microemulsion, was investigated as a vehicle for lipophilic drugs used in reducing the risk of heterosexual transmission of STDs [71]. Liposomes are well established as a novel vaginal delivery system, able to effectively deliver entrapped drugs for an extended period of time at the site of action [54, 59].

Vaginal Ring: The vaginal ring technology offers an innovative platform for a convenient delivery of hormonal agents. [60]. The vaginal ring is a torous shaped device made of a silicone elastomer which contains drug released by diffusion through the elastomer. Ring design, solubility of drug in the elastomer and the molecular weight of the drug are important factors that regulate the release pattern of the drug. Very high release rates can be attained by using a high drug load at the ring surface. Moderately high release rates may be attained by coating a homogeneous ring. If an even lower release rate is desired, the drug may be confined to a small diameter at the center of the ring (core ring). The vaginal ring technology has the capacity to deliver a relatively constant dose of drug intravaginally over an extended period of time in a single application [60], to treat conditions such as depression, eating disorders, migraine headache, pain, premenstrual dysphoric disorders (PMDD) and obsessive compulsive disorders.

METHODOLOGY IN EVALUATION OF VAGINAL DRUG DELIVERY SYSTEM

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 [72].

In Vitro and In Vivo Studies

These studies include the determination of drug release and bioadhesive characteristics in addition to various physical and chemical properties of formulations [73]. 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 [74]. The bioadhesive strength of the vaginal formulation can be measured by various techniques [75].

In vivo studies are conducted in different animal models to assess efficacy, distribution, spreading and retention of formulations in the vagina [76]. Gamma scintigraphy and colposcopy [77] 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 [78].

Several animal models such as sheep, rats, rabbits, rhesus monkeys, macaque monkeys, dogs and mice have been used in different studies in the development of vaginal formulations [79]. 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 [80].

CONCLUSION

Over the years, the vaginal route has been used for the local application of drugs, but is now

becoming a potential route for noninvasive, controlled transmucosal delivery of both local and systemic therapeutically active compounds. The safety and efficacy of vaginal administration have been well established. 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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