Vaginal Mucosa – A Promising Site for Drug Therapy

Vinita Vijay Kale1* and Alok Ubgade2

1Department of Pharmaceutics, Gurunanak College of Pharmacy, Nagpur, India.
2Department of Pharmacology, Gurunanak Technical Institute, Nagpur, India.

Authors’ contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

ABSTRACT

The vagina provides a promising site for local effect as well as systemic drug delivery because of its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs and self-insertion. The pharmaceuticals currently used for vaginal delivery includes those that provide protection against viral infections, including Acquired Immune Deficiency Syndrome (AIDS) and other sexually transmitted infection (STDs). The anti infectives used in treatment of vulvovaginal infection, and vaginitis includes chemicals, for example, clotrimazole, miconazole, clindamycin, sulfonamide and probiotics. Currently, there is a variety of pharmaceutical products available on the market designed for intravaginal therapy (tablets, creams, suppositories, pessaries, foams, solutions, ointments, intravaginal rings, films and gels). However, their efficacy is often limited by a poor retention at the site of action due to the self-cleansing action of the vaginal tract. The vaginal cell lining is covered with a viscous and elastic gel. The physicochemical properties of this gel can influence the rate of diffusion from the bulk to the site of absorption. The choice of absorption model depends totally on the questions to be answered with respect to the test compound being studied. Having studied this review, thus one should able to: understand the anatomy and physiology of the vagina as site of drug administration; understand the pharmaceuticals preferred for administration via vagina; understand the different vaginal delivery system; understand the in vitro models to study vaginal permeability.

*Corresponding author: Email: kvinita@rediffmail.com, alokmubgade@yahoo.co.in;
Keywords: Vaginal drug delivery; vaginal epithelium; permeability; vaginal products; evaluation of vaginal products; vaginal infection; microbiota of vagina.

1. INTRODUCTION

In recent past the focus of research in drug discovery and development are twofold. First, in finding new drug delivery system or finding a new site of administration of the drugs. Secondly, the new delivery system must provide a huge degree of safety and optimum efficacy. In last decade extensive efforts have been made towards the administration and absorption of drugs via vaginal route. The potential of vagina as a site of drug administration has been well established [1,2]. Traditionally this route of drug administration was important for local treatment of gynaecological conditions such as infections and in hormonal therapy [3]. The vaginal route being non-invasive provides several advantages such as self-administration, reducing or eliminating the incidence and severity of side effects. Of late the vagina has gained recognition as potential route for systemic drugs because of its drug absorption properties. The properties such as large surface area of vaginal mucosa, permeability of vaginal mucosa, dense network of blood vessels and ability to by-pass first pass liver metabolism has made it excellent route of drug administration to achieve the desired drug effects [4].

The vaginal ecosystem is a finely balanced environment maintained by a complex interaction among vaginal flora, microbial by-products, estrogens and host factors. The vagina is usually resistant to infection for two reasons- marked acidity and a thick protective epithelium. Insults that affect the vaginal microbiology, vaginal epithelium, or vaginal pH lead to an increased susceptibility to vaginal infections.

The administration of a dosage form via vaginal route can result in either local or systemic delivery or both. The successful delivery of the drugs through vagina represents a pharmaceutical challenge for several reasons. The major reason being, vagina has unique features in terms of microflora, pH, hormonal cyclic changes, permeability perfusion time etc. These factors must be considered during the development and evaluation of vaginal drug delivery systems [5]. A well designed vaginal product depends on the vehicles (base) that effectively deliver the active pharmaceutical ingredient (drug) in a pattern that does not destroy the pharmacological agent and is simultaneously safe for the patient. There are varieties of products available in the market for vaginal administration that includes creams, tablets, gels, pessaries, suppositories, films, rings and douches [6,7]. The choice of route of administration is primarily influenced by location of the biological target. If the target is external or easily accessed then local delivery of the medication is effective approach [8]. Literature survey has revealed that locally acting drugs used in vagina includes antibacterial [7], antiprotozoal [9], antifungal [10] and antiviral [11]. Whereas, for systemic effects the drugs used includes bromocriptine, sildenafil, oxytocin, calcitonin, LHRH, insulin, human growth hormone etc [12].

In-vitro dissolution studies are an essential tool during the early and late stage drug development [13]. The quality of the in-vitro dissolution data are of great importance for their proper use in the evaluation of dosage form performance. Similarly the penetration of chemicals through vaginal mucosa can be characterized using both in vivo and in vitro methods [14].
2. VAGINA AS A SITE OF DRUG DELIVERY

Vaginal route serves as a potential site of drug administration for local and systemic absorption of a variety of therapeutic agents. Intravaginal drug delivery has been traditionally restricted to delivery of antifungals to the local vaginal cavity. The understanding of vaginal physiology has led to the design of specific intravaginal drug delivery systems to reach the systemic circulation. The mucosal lining of vagina mainly has the protective function. The absorption of drugs in vaginal route is similar to other mucosal routes. The absorption of drugs through mucosa occurs by three mechanisms viz., transcellular via concentration dependent diffusion through cells; paracellularly by mediation of tight junction and or vascularly or through receptor mediated transport. In vagina the absorption of drugs occurs through two steps: drug dissolution in the vaginal space and across the membrane by permeability. Therefore the factors that affect drug dissolution and permeability (membrane transport) would affect the absorption profile of vaginal drug delivery systems [15].

2.1 Anatomy and Histology of Vagina

The vagina is a female reproductive organ. In the literature vagina is described as a slightly S- shape fibro-muscular, tubular organ about 6-10 cm long and extended from the cervix of the uterus to the vestibule [16]. The anterior surface of the vagina is in relation with the fundus of the bladder, and with the urethra and the posterior surface is separated from the rectum.

Histologically vagina consists of an internal mucous lining and a muscular coat separated by a layer of erectile tissue (Fig. 1). The mucus membrane is continual lining the uterus (Table 1). The epithelium covering the mucus membrane is of stratified squamous cells similar to those of buccal mucosa. The vaginal epithelium is comprised of five different cell layers- (i) superficial layer whose thickness varies with age and hormonal activities [16]. (ii) the next is lamina propria or tunica, made of dense connective tissues consisting of collagen and cells such as macrophage, mast cells, lymphocytes, neutrophils, eosinophils etc. It contains a network of nerve fibres, lymphatic drainage system and blood supply. It is suggested that the drugs can gain entry into the systemic circulation through the blood vessels of lamina propria. The submucous tissue is very loose and contains numerous large veins. The surface of mucosa has number of folds or also called as rugae which increases the surface area of the vaginal wall (iii) the muscular coat consists of two layers- an external longitudinal, and an internal circular layer. (iv) external to muscular coat is a layer of connective tissue containing large plexus of blood vessels The surface of vagina has many folds (called as rugae). The rugae increases the surface area of the vaginal wall [17]. The vagina is highly vascular; a plexus of arteries and veins is located round the vagina [18]. The venous blood supply from the vagina does not enter the portal system and therefore first-pass metabolism does not occur. This makes the vagina an useful site for the systemic administration of the therapeutic agent.
Table 1. Histological description of human vagina

<table>
<thead>
<tr>
<th>Layers</th>
<th>Sub-layers</th>
<th>Histological Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td>Epithelium</td>
<td>Multiple layer thick made up of non-keratinized stratified squamous cells of five different types viz., basal cells; parabasal cells; transitional cells; intermediate largest cells and superficial outermost layer.</td>
</tr>
<tr>
<td>Lamina Propria</td>
<td>Consists of loose connective tissues that contain blood vessels and lymphatics.</td>
<td></td>
</tr>
<tr>
<td>Submucosa</td>
<td>Consists of connective tissue made of collagen fibres, elastic fibres and blood vessels.</td>
<td></td>
</tr>
<tr>
<td>Muscularis</td>
<td>---</td>
<td>Consists of muscles fibres arranged in outer longitudinal layer and an inner circular layer.</td>
</tr>
<tr>
<td>Adventitia</td>
<td>----</td>
<td>Consists of thin fibrous layer made of collagen fibres, elastic fibres and blood vessels.</td>
</tr>
</tbody>
</table>

2.2 Environment of Vagina

The vagina serves as a passage between the outside of the body and the inner reproductive organs. Although vagina has no glands, the vagina produces large amount of fluid [17]. The vaginal fluid is a transudate through the vaginal epithelium (the cervical mucus) and from the endometrium and uterine tubes [19]. The vaginal secretion is a mixture of several components such as proteins/peptides, glycoproteins, lactic acid, acetic acid, glycerol, urea,
glycogen and ions such as Na$$^{+}$$, Ca$$^{++}$$ and Cl$$^{-}$$ [20]. The vaginal epithelium cells of fertile women release glycogen which supplies nutrition to commensal bacteria Lactobacillus. These bacteria degrade glycogen to acid and thereby create acidic environment which restricts the growth of the pathogenic microorganisms [21]. The pH of normal fertile woman is in the range of 3.5 to 4.5 or a value of 4.2. The vaginal pH changes with age, stages of the menstrual cycle, infections and sexual arousal (Fig. 2). In the post menopausal period in a woman’s life the vagina secretion decreases by 50% compared to woman in reproductive age [22].

![Fig. 2. pH during different phases of woman life](image)

The pH of the vagina and the thickness of vaginal membrane is important in terms of the design and the efficacy of drug delivery systems. The epithelial layer changes its thickness by about 100-200 µm as estrogens level changes [17]. Before ovulation the epithelium is the thickest (250) and becomes thinner (150 µm) during the secretory phase of the menstrual cycle. After menopause, the thickness of the vaginal wall decreases resulting in an increased permeability of the epithelium [19]. The vaginal pH and membrane thickness can be altered using oral contraceptives [23]. The change in the vaginal pH is observed during pathological conditions such as infections and inflammations. Diseases such as Candida vaginitis generally lowers the pH, whereas, the inflammatory vaginitis elevates the pH towards neutrality [24]. The amount of vaginal fluid increases during menstrual cycle. This means that fluctuation in vaginal bioavailability can occur. The systemic absorption of drug when administered through vagina depends on two factors- the dissolution of drug particles in the vaginal fluid and the degree of deactivation of enzymes in the fluids [25]. The presence of vaginal fluid can reduce the overall efficacy of vaginal product either cause of dilution or increase leakage or decrease in residence time. Different enzymes are present of which the proteases seem to be the prominent barrier for the absorption of intact peptide and protein drugs into the systemic circulation [26]. Most enzyme activity exists in the external layers and the basal cell layers of the vagina.

2.3 The Microbiota of Vagina

The human vagina is inhabited by a range of microbes from a pool of over 50 species [27]. The normal microbiota consists of a wide variety of genera and species, both aerobic and
anaerobic. A summary of the major species observed is presented in (Table 2). The microbiota of premenopausal woman varies than those who have gone through menopause. *Lactobacillus* species dominates the vagina of premenopausal woman and remain the organisms of most importance to vaginal health [28]. The presence of Lactobacilli is directly related to the glycogen content. During reproductive life, from puberty to menopause, the vaginal epithelium contains glycogen content due to the actions circulating estrogens. The Lactobacilli species metabolize glycogen to lactic acid and other products of metabolism and inhibit colonization of vagina by exogenous microbes. Thus, postmenopausal women are more susceptible to urogenital infections. Any change in the environment or composition of vagina makes it very susceptible to infections. The three most common diseases associated with the vagina are – vaginitis, trichomoniasis and candidiasis [29].

<table>
<thead>
<tr>
<th>Species</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Garnerella vaginalis</em> [31]</td>
<td>Very common organism in vagina. These are facultative anaerobes causing vulvovaginitis</td>
</tr>
<tr>
<td><em>Lactobacilli sp.</em> [32]</td>
<td>Very common organism in vagina. It is the major constituent of the vaginal flora.</td>
</tr>
<tr>
<td><em>Neisseria sp.</em> [33]</td>
<td>Common organism in vagina. It is associated with the STD gonorrhoea.</td>
</tr>
<tr>
<td><em>Staphylococcus sp, Proteus sp.</em> [34]</td>
<td>Common organism in vagina. 5% of the women show the presence of these organisms. Overgrowth can cause toxic shock syndrome.</td>
</tr>
<tr>
<td><em>Mycoplasm hominis</em> [35]</td>
<td>Common organism in vagina. It is linked with premature labor and birth and associated with bacterial vaginosis.</td>
</tr>
<tr>
<td><em>Trichomniasis sp.</em> [36]</td>
<td>It is a common protozoa in vagina. It is characterized by yellow-green discharge and vulvolar irritation.</td>
</tr>
</tbody>
</table>

### 2.4 Drug Release Across the Vaginal Membrane

For systemic absorption, a drug must pass from the absorption site through or around one or more layers of vaginal lining to gain access into the general circulation. The drug permeation across the epithelial barrier of vagina is via two main routes-the paracellular route and, the transcellular route [37]. The transcellular movement of the drug is the process of movement across epithelial cells. Some molecules such as polar molecules may not be able to move across the cells but instead, go through gaps of tight junctions between cells (paracellular absorption). Transcellular passage involves the movement of drug across the epithelial membrane by active or passive diffusion or via endocytic process [38].

The paracellular transport is generally suitable for small molecules as it follows diffusion mechanism and the rate follows Fick’s law. The small molecules, hydrophilic as well as hydrophobic (lipophilic), drugs can traverse paracellularly. For most drugs that are lipophilic, transport occur transcellularly via passive diffusion across epithelial membrane [39]. The movement occurs down the concentration gradient following Fick’s law of diffusion. Fick’s
law of diffusion correlates with the lipid solubility or ionized state, particle size, permeability and surface area of membrane across which the transport is occurring.

If the general account of cyclic changes that occur in vaginal epithelium is considered, a profound effect on absorption or transport of drug across vaginal membrane can be observed [17]. The permeability of the vaginal membrane to the drug molecule i.e., the permeability coefficient \( P = \frac{C_{\text{oil}}}{C_{\text{water}}} \) of the drug, will contribute to the movement of drug by transcellular mechanism. The permeability of vaginal membrane is sum total of the lipid pathway and the pore pathway [40]. The lipophilic drugs have the high permeability coefficient for their transcellular transport across the epithelial cells. The physiological changes in the thickness of the vaginal membrane that occurs during the menstrual cycle influence the transport of hydrophilic drugs [41]. During metestrous and diestrous phases of menstrual cycle the epithelium barrier becomes thin and there is pore like widening of the intercellular channels resulting in the movement of even high molecular weight hydrophilic drug across epithelial membrane [42].

3. PHARMACEUTICAL ASPECTS OF VAGINAL DRUG DELIVERY SYSTEM

Drugs are often given to a patient as a finished dosage form that includes the active pharmaceutical ingredient, and selected substances that make up the dosage form. The common vaginal dosage form includes tablets, capsules, suppositories, intravaginal rings and topical drug products [43]. The formulation and development is critical to the success of a pharmaceutical product. The formulation and manufacture of a drug product requires a thorough understanding of not only the physiological properties of absorption site but also the physicochemical properties of the active drug substance (Table 3) [44]. The physical and chemical behaviour of a substance is called as its physicochemical properties. There are many pharmaceuticals that are being focussed to be developed in vaginal drug delivery system (Table 4).

Table 3. Physiological and physicochemical factors affecting vaginal delivery systems

<table>
<thead>
<tr>
<th>Vaginal physiology</th>
<th>Formulation factor affected</th>
<th>Effect at administration site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal axis due to women posture</td>
<td>Residence time, Drug distribution</td>
<td>The API may leak out due to gravity, Entire vaginal cavity not accessible difficulty in homogenous distribution.</td>
</tr>
<tr>
<td>Surface area (rugae)</td>
<td>Drug absorption rate</td>
<td>Increase in the surface area and hence absorption rate.</td>
</tr>
<tr>
<td>Vaginal fluid</td>
<td>Amount of soluble drug</td>
<td>It varies throughout menstrual cycle.</td>
</tr>
<tr>
<td>Presence of Mucus</td>
<td>Drug permeability</td>
<td>Thick mucus less permeable and thin mucus more permeable thus vary in absorption.</td>
</tr>
<tr>
<td>Epithelium thickness</td>
<td>Drug permeability</td>
<td>Thick epithelium less permeable and thin epithelium more permeable thus varies in absorption.</td>
</tr>
<tr>
<td>pH</td>
<td>Solubility and stability of drug</td>
<td>Ionic state of drug may change due to change in pH and this will affect the solubility, absorption and stability of drug.</td>
</tr>
</tbody>
</table>

989
Table 4. Some popular active pharmaceuticals (drugs) used for vaginal administration

<table>
<thead>
<tr>
<th>Active pharmaceuticals</th>
<th>Solubility</th>
<th>Drug property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonoxylon</td>
<td>Water soluble</td>
<td>Nonoxynol 9 is a surfactant spermicide used for contraception in spermicidal creams, jellies, foams, gel, and lubricants. It is also used in conjunction with other methods of contraception, including condoms, cervical caps and diaphragms.</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Lipid soluble</td>
<td>An imidazole antifungal agent that is used topically. Estradiol-17-beta is the most potent form of mammalian estrogenic steroids.</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Lipid soluble</td>
<td>Estradiol-17-beta is the most potent form of mammalian estrogenic steroids.</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Lipid soluble</td>
<td>It is synthetic progesterone analog and used as contraceptive.</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>Soluble in water</td>
<td>It is a progesterone and used as contraceptives.</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>Water Soluble</td>
<td>It is used in hormonal manipulation.</td>
</tr>
<tr>
<td>Progestrone</td>
<td>Highly soluble in water</td>
<td>It is used as contraceptives.</td>
</tr>
<tr>
<td>Oxyquinoline sulfate</td>
<td></td>
<td>It is used in along with acetic acid for destroying or slowing the growth of organisms that cause vaginal infections.</td>
</tr>
<tr>
<td>Gonadorelin LHRH</td>
<td>Water Soluble</td>
<td>Used in vaginal dryness etc.</td>
</tr>
<tr>
<td>Prostaglandin E2 LHRH</td>
<td>Lipid soluble</td>
<td>Used for induction of labour</td>
</tr>
<tr>
<td>LHRH</td>
<td>----</td>
<td>Pubertal development</td>
</tr>
<tr>
<td>Insulin</td>
<td>Freely soluble in water</td>
<td>Used as antidiabetic</td>
</tr>
</tbody>
</table>

3.1 Physicochemical Properties of Drug Substances

The physicochemical properties of the drug substances directly affect the bioavailability of the drug substance. These properties include, drug pKa, lipid solubility, partition coefficient, and particle size. The natural pH environment of vaginal tract is towards acidic pH [45]. Most drugs are either weak acids or weak bases. This infers that some drugs are ionized to certain extent that is determined by their pKa and pH of the biological fluid. In accordance with the pH-partition hypothesis, the unionized form of a drug with larger values of oil/water partition coefficient is better absorbed (transported across the vagina membrane) than the ionized form. The slight acidic pH of vagina favors the greater absorption of acidic drugs (pH< pKa), while basic drugs are better absorbed when pH is slightly alkaline (pH> pKa). On the contrary, the ionized form of a drug substance display greater solubility than the unionized form. A drug gets absorbed in the biological system, when it gets dissolved (ionized state) in the physiological fluid at the absorption site. Solubility of basic drugs at vaginal pH can be increased by reducing the particle size (by micronization) of the drug. Small particles exhibit greater effective surface area, thus, more intimate contact between solid surface and aqueous solvent resulting into higher dissolution rate which increases its absorption efficiency. The drug solubility is also a function of the geometric shape, the crystalline, hydrate, or salt form of the drug. In general, the amorphous form of the drugs are more soluble than the crystal form of same drug; the anhydrous forms are more soluble than hydrate forms [46]; and the salt form of lipophilic drug is more soluble than its free form.
3.2 Selection of Excipients to be used in Dosage Form

A careful selection of excipients can lead to the development of formulations that are both effective and economical. Traditionally, the excipients that are not active pharmaceuticals are known to be inactive ingredients. The vaginally administered active substances and formulations are mainly used for the treatment of local infections and only few are used for systemic absorption [4].

Once a medication is inserted or applied to the target area, the drug must leave the dosage form for absorption. The susceptibility of the drug to migrate from the formulation to the application surface is affected by factors such as lipophilicity of the vehicle, drug solubility in the formulation, and effects of additives on the barrier properties of the mucosal surface. Excipients that increase the aqueous solubility of the active substance generally increase the rate of dissolution and absorption. The addition of surface active agents may increase the wetting, solubility and absorption of active substances. Surfactants may enhance partitioning by reducing the surface tension between the vehicle and the membrane surface and by influencing the barrier potential of the membrane and the tight junctions. It may also disrupt the barrier layers of the membrane [47]. Beta-cyclodextrin, citric acid, Tween 80 and Polaxamers are added in vaginal formulation to increase drug solubility. Excipients that are bioadhesive or that swell on hydration can promote absorption by increased contact with epithelial surfaces or by prolonging residence time [17]. The bioadhesive agents that are being tested for vaginal formulations includes- alginites, carbomer, chitosan, xantham gum that shows specific mucoadhesion properties [48,49]. Many physical and enzymatic barriers can prevent successful delivery of active pharmaceutical ingredients. Materials used to enhance its permeability have ranged from simple solvents such as ethanol or propylene glycol to aromatic chemicals such as terpenoids. Such penetration enhancers appear to work by disrupting the lipid domains that reduce permeability [50]. Chemical enhancers often studied or used are bile salts, chelators, alcohols and fatty acids that may exert their effect by: altering the rheological properties of the mucus layer; enhancing transcellular transport by interacting with phospholipids and/or proteins to increase membrane fluidity; inhibiting enzyme activity [51].

3.3 Vaginal Products

Various vaginal dosage forms available in the market are solutions, suppositories, creams, ointments, gels, foams, sprays, tablets, capsules, etc [52]. Ideally vaginal products are designed for local effect and thus should distribute uniformly throughout the site of action. There are several functional qualities into a vaginal drug delivery system. The qualities include the following: prolonged retention to minimize; ability to solubilize water soluble and semi-water-soluble drugs; usefulness in both pre- and postmenopausal women.

3.3.1 Vaginal gels

The most conventional vaginal drug delivery systems are gels. Gels are easy to manufacture and can spread onto the surface of mucous. The rheological properties of gel and its water content provides advantage of hydration and lubrication which is essential as in some pathological situations vagina is characterized by dryness of the vaginal mucosa [53]. The addition of mucoadhesive polymer in gel formulation can improve the time of contact thereby preventing the leakage or loss of active and also for prolonging the effect.
3.3.2 Vaginal tablets

In the market are available several antibiotic tablets for vaginal delivery. Tablets are designed to rapidly disintegrate in the vaginal cavity to release the active drug. The normal vaginal tablets contain similar components as like the conventional oral tablets. Mucoadhesive polymers are sometimes used in vaginal tablet formulations to overcome the drawback of normal vaginal tablet i.e., to improve residence time [54]. Literature shows that presence of hydrophobic and release retarding material may decrease the absorption of a drug from the vaginal environment. Thus, the addition of penetration enhancers such as surfactants becomes useful in the vaginal formulations.

3.3.3 Vaginal rings

Vaginal rings are circular ring type drug delivery devices designed to release drug in controlled release fashion after insertion in the vagina [55]. These are 5-6 cm in diameter where active substances are homogenously dispersed. Vaginal rings are mainly designed in reservoir and sandwich type of system to deliver mainly the contraceptive and in hormonal replacement therapy.

3.3.4 Suppositories/pessaries

Vaginal suppositories/ pessaries are similar to the rectal suppositories and used mainly for local infection, vaginal atrophy or for contraceptive purpose. In addition the vaginal suppositories may be used to achieve systemic absorption of active substances. Vaginal suppositories are formulated using either water soluble or water miscible bases [56]. Water soluble bases are also called as glycerol-gelatin base. These bases are used for the formulations that contain water soluble active substances. Selection of gelatin becomes very important in glycerol-gelatin suppository formulation. The isoelectric point of type A gelatin ranges between 4.7- 5.3 and the pH of aqueous solution in the vagina will affect the ionization of the active substance, particularly when they are either weakly acidic or weakly basic. Water miscible bases are comprised of PEG’s (polyethylene glycols). Following insertion into the vagina the vaginal pessaries do not melt but due to their hygroscopicity will instead dissolve. The successful formulation of the suppositories may require the addition of other excipients. These excipients include– surface active agents, agents that may reduce hygroscopicity, which can control the melting or dissolution of bases and the preservatives.

3.3.5 Novel vaginal drug delivery systems

As the advancement in pharmaceutical technology, the new drug delivery systems are replacing the traditional delivery systems. In the past vaginal delivery preparations were restricted to topical drugs. In recent pass the focus of pharmaceutical industries is to bring the vaginal delivery systems that contains special drugs such as prostaglandins, insulin, progesterone or newer anti HIV that are either locally or systemically active and absorbed. The natural progesterone given orally as replacement therapy have few drawbacks such as risk of endometrial cancer, low bioavailability, lack of efficacy and high levels of metabolites that have CNS effect. These limitations can be overcome by vaginal administration of progesterone in conventional formulations. In a study Vaginal progesterone replacement with the polycarbophil gel preparation was as effective as IM progesterone in producing clinical and ongoing pregnancies within our donor egg program in the dosages administered. CRINONE (Progesterone gel) is one such marketed bioadhesive vaginal gel containing micronized progesterone in a diluted emulsion system [57]. In another study absorption and
release of progestin incorporated in the vaginal rings made of plastic polymer was conducted [58]. It was observed that steroid was released at constant rate and absorbed directly through the vaginal epithelium into the systemic circulation. This delivery system provides many advantages over oral contraceptives (OCs), including avoidance of the first-pass effect through the liver, constant serum steroid levels, longer duration of use, and greater bioavailability of the hormones. CVRs (Contraceptive Vaginal Rings) containing progestin only are designed for continuous use for 3 to 6 months.

Prostaglandin (PGE$_2$) is an agent used to ripen the cervix for the induction of labour, or for second trimester abortion [53]. Vaginal controlled- release hydrogel formulation containing prostaglandins are designed for this effect. The possibilities of delivering therapeutic peptides are continuously being researched. Large molecular weight peptides, such as insulin, TSH, calcitonin, GnRH analogs have demonstrated systemic absorption via vaginal route. In one of the study vaginally administered insulin was suspended in a polyacrylic acid aqueous gel base was investigated and the plasma insulin reached a peak, and prominent hypoglycemic effects were observed during the first 30 min [59]. Recently, it has been obtained normal ovulation rates in rabbit inseminated which were induced with an intravaginal dose of GnRH analogue [60]. In similar study buserelin and triptorelin demonstrated ovulation in rabbit females by absorption through the vaginal mucosa when administered and vehiculated in the seminal dose, avoiding i.m. administration [61]. Until recently, formulation approaches for HIV microbicides were limited to gel formulations. Although microbicide gels are economical to use but they show poor vaginal retention and requires the use of applicator. Moreover vaginal gel is required to be applied prior to every act of intercourse. Few HIV non-gelled micobicide delivery systems currently under research can show not only improved efficacy but also acceptability than gel based formulations. Vaginal rings such as Estring, Ferming or Nuvaring are introduced in the market for continuous long term vaginal delivery of HIV micobicide [62].

Follicle Stimulating Hormone (FSH) has been widely employed for ovulation induction and in-vitro fertilization. Ovulation induction is dependent on the plasma level of FSH achieved after daily dose of intramuscular/ subcutaneous injections. Recently recombinant human FSH (rhFSH) preparations are introduced to reduce the number of visits to the clinic [63]. This treatment regimen employs the concept of mesotherapy and first uterine pass effect, targeting to the uterus as FSH receptors are located on the somatic cells of uterus. In mesotherapy small dose of rhFSH is administered at correct location (i.e. subcutaneous layer of vagina) every 3 days and show higher rate and extent of absorption.

4. EVALUATION OF VAGINAL PRODUCTS

Investigation of the passage of drugs or chemical substances across various biological membranes is of high importance in designing systems for best drug delivery. The penetration of chemicals through vaginal mucosa can be characterized using both in-vitro and in-vivo methods. Dissolution and subsequent permeation through vaginal epithelia are process in vaginal absorption whereby each of those may be rate limiting. Several limitations affect both the processes such as ample wetting, appropriate swelling and disintegration of dosage form, dissolution of active compound, residence time depending on the surrounding microclimate conditions such as pH, enzymes, microbiota etc.

In-vitro dissolution testing is a requirement for all dosage forms and is used in all phases of development for drug release from the product and its stability testing. Dissolution is considered as surrogate of drug bioavailability. At early stages of development, in- vitro
dissolution testing guides the optimization of drug release from the formulation. For dissolution testing, many successful efforts have been made to imitate more and more closely the physiological surrounding of the vaginal cavity.

In the compendia method for determining the dissolution time for a vaginal formulation, the formulation is hanged into a beaker containing dissolution fluid that is stirred with a paddle rotator. The drawback of this method is the volume of dissolution fluid is large, there is no control of the mass-medium interface ratio, and it cannot simulate the in vivo environment [64]. In order to control the mass-medium ratio few other the models have been developed. In one such model wire-mesh basket or a membrane was designed to separate the sample chamber and the reservoir [65,66]. But these models also used large volume of fluid. The flow-cell apparatus holds the sample in place with cotton or wire screen or glass beads [64] in an upright position. Recently, Kale et al. [67] developed a model that almost simulates the environment of the vagina. This model successfully demonstrated actual positional axis of the vagina, the release of probiotic from the product, the maintenance of 37°C temperature (body temperature), small volume of dissolution that exists in vagina and the discharge or the leak volume that comes out of the vagina once the product is inserted in the cavity. The detailed design of this model is shown in (Fig. 3). The Kale et al model also eliminates the risk of exposure of the vaginal formulation to agitation and sampling device that otherwise exists in other models.

![Design of a dissolution apparatus for vaginal formulations containing probiotics](image)

**Fig. 3. Design of a dissolution apparatus for vaginal formulations containing probiotics**

1-Inlet for MRS medium (5ml), 2-Inlet for warm water (37C), 3-Outertube (4cm), 4-Inner Tube (1.5 cm), 5-Vaginal tablet, 6-Cellophane membrane, 7- Outlet for warm water, 8- Collecting vessel.

*In-vitro* absorption or permeability model that estimates the permeability across biological membranes provide a valuable tool for determining factors limiting the potential absorption and bioavailability of drugs [68]. In general, amongst the several, few technologies or models that are used to study the permeability of the drugs across the intestinal epithelia can be used to predict the bioavailability of drug when administered as vaginal product. *In-vitro* permeability methods are generally conducted using a diffusion-cell system with either a static or flow-through cell method. The different flow cells as shown in (Fig. 4) include the conventional static Franz cells, the Ussing chamber as well as flow-through diffusion cells [68,69,70]. All the three types of permeability models contain a donor and acceptor
compartment, between which a membrane that are frequently used for permeability of drug substance include excised human tissue or artificial membrane. Franz cells and the Ussing system, that are static models, are regularly used in permeability studies. Both these models are labour intensive, since an accurate volume of sample must be removed at fixed time intervals from the acceptor compartment with a simultaneous media replacement to maintain sink conditions in the cells. The manual sampling requires constant attention and is therefore often limited to the normal laboratory hours which mean a less accurate fitting of the curve. The flow-through diffusion cells offers automation with the addition of a pump that offers an accurate, constant flow rate of buffer. A flow-through diffusion cell method, by virtue of continuous replenishment of perfusion medium, helps in maintaining the viability of the skin tissue/mucosa and thus would mimic better a physiological environment than a static cell. The drug is added to the donor compartment of the flow cell and collected by means of a fraction collector from the acceptor compartment of the flow cell. This is done for the required time period of the experiment, at a constant flow rate.

More recently monolayer system also called as Caco-2 culture system is used as membrane to perform the permeability studies of the drug once released from the product in the physiological environment. Monolayer systems consist of a tight cell layer grown on a porous support to separate two fluid compartments (Fig. 5). They are widely regarded as the most sophisticated in vitro tools for medium to high-throughput modeling of important pharmacokinetic barriers, such as intestinal epithelium, blood-brain barrier, or any other physiological barrier etc [71].

Fig. 4. In-vitro membrane permeability models (A) franz diffusion cell (B) ussing chamber
5. CONCLUSION

Product market of novel drug delivery systems has increased significantly in last few years. Several protein and peptide based drugs are either introduced or are in the pipeline to enter into the market. The challenge listed by the scientists to develop these complex therapeutic agents is to find suitable delivery system. These newer therapeutic agents are unique in nature and finds difficulty in delivery through conventional routes. Future research is therefore focused on delivery of complex therapeutic agents through different routes of administration such as nasal, pulmonary, rectal or vaginal.

The anatomical position, rich blood supply and large surface area of vagina make it suitable as delivery site for drugs acting locally or systematically. In oral route the drug has to reside in gastrointestinal tract which is sight for most drug interactions. However, in vagina such interactions are not observed. Hence, compared to oral cavity, vagina is better route for delivery of hormones and microbicides. The absorption of drug across membrane can prevent the possibility of hepatic first pass metabolism. With these advantages the vaginal drug delivery systems have grown to become important for pharmaceutical companies in recent years. This review would provide thorough insight for those who want to work in this research area.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.
REFERENCES

51. Viljoen I, Van Zyl JM, Van der Bijl P. The role of surfactant in, and a comparison of, the permeability of porcine and human epithelia to various chemical compounds. M.Sc. Thesis, Stellenbosch University; 2005.


© 2013 Kale and Ubegde; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?id=234&id=14&aid=1896