International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 2; March 2018; Page No. 97-106

Recent approaches in vaginal drug delivery systems

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Abstract
Vaginal delivery is an important route of drug administration for both local and systemic diseases. The vaginal route has some advantages due to its large surface area, rich blood supply, avoidance of the first-pass effect, relatively high permeability to many drugs including large molecular weight drugs, such as peptides and proteins and self-insertion. The vaginal route appears to be highly appropriate for bioadhesive drug delivery systems in order to retain drugs for treating largely local conditions, or for use in contraception. In particular, protection against sexually-transmitted diseases is critical. To prolong the residence time in the vaginal cavity, bioadhesive therapeutic systems have been developed in the form of semi-solid and solid dosage forms. This review, therefore, summarizes various vaginal drug delivery systems with an introduction to vaginal physiology, factors affecting drug absorption from the vaginal route, applications and also provides an overview of various currently available vaginal drug delivery systems in the market.

Keywords: intra vaginal delivery, vaginal formulations, vaginal tablet, vaginal rings, vaginal films, vaginal creams, vaginal gels, suppositories

Introduction
Vaginal drug delivery system refers to the system in which drug formulations are directly applied in vaginal cavity for producing local action. It is an important route of drug administration for both systemic and local effect. The drug formulations contain bio adhesive polymers, due to which drug formulations remain attached to the vaginal mucosa for longer periods and release drug in controlled rate. Thus vaginal route is used to treat vaginal infections, to prevent the sexually transmitted diseases or for contraception. The main advantages of vaginal route are local effect, large surface area, rich blood supply, avoidance of the first pass effect and self-insertion.

In this era of pharmaceutical research, the field leading is the development of novel drug delivery system for drug molecules which already exist so that their efficacy is maximised with better patient compliance and reduced adverse effects. With the advancement in technology of drug delivery there has been a wider choice of sites for drug administration. Vagina, as a site for drug delivery, has certain advantages due to which it has been exploited in order to achieve desirable therapeutic effects.

The first formulation which was designed for vagina was to treat local bacterial, fungal infections and inflammations. With the development of novel products for female health, comprising therapeutic substances such as peptides, proteins, antigen there is need for designing high performance intravaginal drug delivery systems. This route provides a better alternative to the parenteral route for drugs. The formulation given by this route include pessaries, tablets, inserts, creams, powders, douches, gels, vaginal rings etc but because of limitations like messiness, leakage and low residence time, there has been poor patient compliance and loss of therapeutic efficacy therefore more stress is laid on the development of Intravaginal controlled release drug delivery system which is an effective means of continuing delivery of therapeutically active agents [1].

Vaginal anatomy, histology and physiology
The vagina is a female genital organ, plays an important role in reproduction. vagina as a slightly S-shape fibro muscular, tubular organ, that approximately 6-10 cm long and extended from the cervix of the uterus to the vestibule [2, 3]. As per radiographic colpographic study vagina is a slightly curved organ with two distinct portions; a lower convex portion and a wider upper portion that lies in an almost horizontal plane at standing position of subject [4, 5]. The angle between upper and lower axes is about 130 degree. When vagina enters to the pelvis region it passes through two diaphragms; the urogenital diaphragms and the pubococcygeus from the pelvic diaphragms, act as sphincters to the vaginal introitus. The women of reproductive age having numerous folds in vagina, named "rugae", which provide distensibility, support as well as increase surface area of vaginal wall [6]. Vagina is mainly consisting of two types of nerve supply. Among this one is peripheral, which primarily supplies to the lower quarter of the vagina and make it a highly sensible area. An autonomic fiber is the other one responds to stretch and are not very sensitive to pain. Due to this only women rarely feel localized sensation or any discomfort when they use vaginal products

like suppositories, tampons, vaginal ring etc., and often unaware of the presence of such items in the vagina [1].

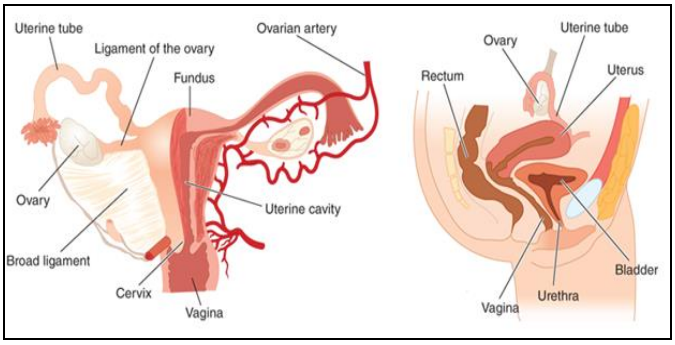

Fig 1: Anatomy of uterus and vagina [7]

The vaginal histology is mainly consisting of four distinct layers. An estimated cell turnover of vagina is about 10-15 layer in order of 7 days. The superficial layer is mainly composed of nonsecretory stratified squamous epithelium; its thicknes varies with age and several hormonal activities. The next is lamina propria or tunica, made of collagen and elastin, which contains a rich supply of vascular and lymphatic channels. The muscular layer is third, with smooth muscle fibers running in both circular and longitudinal directions. The final layer consists of areolar connective tissue and a large plexus of blood vessels [8, 9]. The vaginal physiology is mainly influenced by age, hormonal balance, pregnancy, pH changes and concentration of microflora [10]. Human vaginal fluid mostly transudes from vaginal and cervical cells, which mainly contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl-ketones and aromatic compounds [11].

Advantages of vaginal drug delivery systems

The vaginal drug delivery systems offer following advantages [12, 13]

- This is a better delivery system in case of nausea and vomiting.
- Stomach and intestinal irritation can be avoided.
- Hepatic first pass elimination can be avoided.
- As there is no contact with digestive fluid so enzymatic degradation of drugs is avoided.
- Drug delivery can be stopped by removing the dosage form e.g. Vaginal rings.
- Rapid drug absorption and quick onset of action is achieved.
- When compared to parenteral medication in terms of patient on long term therapy, this system is convenient.
- The vaginal bioavailability of smaller drug molecules is good and in case of larger drug molecule it is improved by means of absorption enhancer.
- It permits continuous and prolonged residence of the dosage form at the site of application.
- 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.

Limitations of vaginal drug delivery systems

Apart from above mentioned advantages this route has several disadvantages too which is listed as follows [14]

- This drug delivery system is gender specific.
- The vaginal route is less preferred because of inconvenience.
- The permeability of the vagina is strongly influenced by the estrogens concentration, which can influence the pharmacokinetics of drugs.
- The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) and this amount is decreasing with increasing age which can affect the vaginal absorption of drugs.
- The pH of the vaginal fluid is also a factor which affects the drug absorption as the unionized drugs absorbed.

Factors considered for vaginal drug delivery system

1. **Vaginal Secretions**

   Though there are no goblet cells in vagina and hence it does not release mucin even then vaginal epithelium is considered as a mucosal surface, vaginal discharge consists of a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, leukocytes, endometrial and tubal fluids. The cervical mucus contains inorganic and organic salts, mucin, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). The volume, viscosity and pH of vaginal fluid may have impact on vaginal drug absorption. The absorption of poorly water-soluble drug is increased when the fluid volume is higher [15]. Whereas presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from vaginal cavity and subsequently reduce absorption [16].

2. **Enzyme Activity**

   The specific enzymatic activity of four different amino peptidases in vaginal homogenates decreases in the order: sheep > guinea pig > rabbit ≥ human ≥ rat [17]. The human genital tract has lower enzymatic activity leading to less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract [6].

3. **Vaginal pH**

   The vaginal pH of healthy women of reproductive age is acidic (pH 5 4–5); which is maintained by lactobacillus convert glycogen from epithelial cells to lactic acid. The changes in pH occur by factors such as age, stages of menstrual cycle, infections and sexual arousal. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase the pH [18]. The vaginal pH should be controlled for successful vaginal delivery of drugs.

4. **Micro flora**

   The factors which influence the ecology of the vagina are glycogen content of epithelial cells, glucose, pH, hormonal levels, and trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. The most prevalent organism in the vaginal environment together with many other facultative and obligate aerobes and anaerobes is lactobacillus. The

human genital tract has lower enzymatic which results in less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract [18].

5. **Cyclic Changes**
   The changes in hormone levels (especially estrogens) during the menstrual cycle lead to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions [19]. The variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes create problem in achieving consistent drug delivery.

Vaginal absorption of drugs

Drugs are transported across the vaginal membrane by the trans cellular route, intracellular route or vesicular and receptor mediated transport mechanisms. A physical model of the vaginal membrane as a transport barrier has been described. 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. The absorption of drugs, targeted for local action in the vagina, is not desirable [20].

Factors affecting the vaginal absorption of drugs

Like other mucosal routes of administration, drugs administered via the vaginal route are absorbed (i) transcellularly via concentration dependent diffusion through the cells, (ii) paracellularly mediated by tight junctions and (iii) vesicular or receptor mediated transport as pointed out by Richardson and Ilium [21, 22].

1. **Physiological factors**
   Physiological factors like changes in the thickness of epithelium layer, cyclic changes, changes in the status of enzyme, hormones, volume of vaginal fluid, alteration of vaginal pH and sexual arousal, as described earlier can potentially affect drug release from any intravaginal delivery system and also alter its rate of absorption. For e.g. vaginal absorption of steroids is affected by the thickness of vaginal epithelium [21]. Literature shows that vaginal absorption of estrogen shows high in post menopausal women compared to premenopausal women [23]. The high volume of vaginal fluid may increase the absorption of poorly water soluble drugs; however the same condition again responsible to remove the drug from the vaginal cavity and subsequent reduction of drug absorption. Further cervical mucus, a glycoprotein gel can possibly be exploited for bioadhesive drug delivery. However at the same time it may serve as a permeability barrier for different drug candidates [24]. Again changes in the pH of vagina will alter degree of ionization of weak electrolytic drugs and affect the release profile of pH sensitive drugs [25].
2. **Physicochemical Factors**
   The physicochemical properties of drugs and polymers like lipophilicity, ionization, molecular weight, surface charge and chemical nature can influence the vaginal drug absorption. Further the affinity and bindings of drug with other related component, introduced to prepare a dosage form is an important factor, which can affect both the mass transfer and bio-diffusion of drugs [26].
   A study on vaginal absorption of polyvinyl alcohol suggested a molecular weight range above which compounds will not be absorbed and low molecular weight lipophilic drugs are preferably more as compared to high molecular weight lipophilic and hydrophilic one, vaginal mucosal surface is very specific in this respect[27]. Since vaginal fluid contains a large amount of water, any drug intended for vaginal delivery requires a certain degree of solubility in water. In fact, data on the human vaginal permeability of drugs with different physicochemical properties is very limited; much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption [28].

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 gynecological conditions. These innovative delivery systems may lead to extended product shelf life making the products competitive in the market place. In order to achieve desirable drug characteristics different approaches are used [29]. The compatibility between the drug and excipient can easily be evaluated by thermal (DSC) and isothermal (HPLC) stress testing [30].

1. **Penetration Enhancers**
   Penetration enhancers are capable of promoting absorption and penetration of drug through the vaginal mucosa by decreasing the penetration barrier [31, 32]. Currently, the most preferred penetration enhancers include non-ionic surface active agents, bile salts, benzalkonium chloride, hyaluronic acid[33] polyethylene glycol, ethoxydiglycol and interesterified stone oil [34, 35].
2. **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 [36]. 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 [37].
3. **Mucoadhesive Agents**
   Mucoadhesive agents permit a close contact of formulation with the vaginal mucosal surface by promoting adherence [38]. 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 [39]. 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 [40]. Polycarbophil 934P

exhibited pH-dependent bioadhesive properties [41].

Classification of intra-vaginal drug delivery system [42]

- Vaginal Tablets
- Vaginal films
- Vaginal creams
- Vaginal gels
- Suppositories or Pessaries

1. Vaginal Tablets

The manufacturing process of vaginal bioadhesive controlled release matrix tablets consist of the preparation of a matrix mixture comprising the pharmaceutically acceptable excipients. The release mechanism is based on drug diffusion through the swollen polymers and progressive erosion /dissolution of the gel matrix. The controlled-release properties of the vaginal tablets may be modified by the presence in the dosage form of soluble and insoluble fillers and by their weight ratio.

The insoluble excipients can be selected from the group of microcrystalline cellulose, calcium phosphate tribasic, dibasic calcium phosphate, calcium sulphate and dicalcium phosphate. Either anhydrous or hydrated dicalcium phosphate is preferred. The soluble excipients can be selected from the group of lactose, sorbitol, xylitol, mannitol, amylose, dextrose, fumaric acid, citric acid, tartaric acid, lactic acid, malic acid, ascorbic acid, succinic acid, polyethylene glycols of various molecular weight, soluble hydroxyalkyl celluloses, polyvinylpyrrolidones, gelatins, sodium carbonate and sodium bicarbonate [43]. Mucoadhesive polymers such as polycarbophil, cellulose ethers, chitosan and polyvinylpyrrolidine are used for the preparation of tablet formulations [44, 45, 46].

Fig 2: Vaginal Tablets

2. Vaginal Films

Another mucoadhesive solid dosage form is film [47]. Vaginal films are polymeric drug delivery systems shaped as thin sheets, usually ranging from 220 to 240 micrometer in thickness. These systems are often square (approximately 5cm X 5cm), colourless and soft, presenting a homogenous surface. Vaginal films are produced with polymers such as polyacrylates, polyethylene glycol, polyvinyl alcohol and cellulose derivatives. A bioadhesive hot-melt extruded film is used for topical and mucosal adhesion applications. The film is made from a precursor composition containing a water-soluble or water-swellable thermoplastic polymer, preferably HPC and/or PEO and a bioadhesive polymer. The film can also contain a therapeutic agent, preservative, buffering agent, antioxidant, super-disintegrant or absorbent, flavorant, colorant, water-insoluble polymer, organic acid, surfactant, film modifier and/or cross-linking agent. A mucoadhesive film formulation which is suitable for delivery of therapeutic agents to vaginal mucosa has been developed [48].

Film composition for delivery of pharmacologically effective agents topically to vaginal mucosa comprises polymer which is hydrophilic, hydrophobic or mixture of both. The polymer is selected from the group consisting of hydroxypropyl methylcellulose, gelatin, alginic acid, alginic acid sodium salt, pectin, collagen, poloxamer, carbopol, microcrystalline cellulose, polyacrylic acid, polyethylene glycol and polypropylene glycol. The film has a controllable rate of gelling, swelling and degradation and is preformed into a device or is applied as a coating to the surface of a more complex drug delivery system. pH-Responsive film for intravaginal delivery of a beneficial agent has been prepared for the intravaginal administration of prophylactic and therapeutic agents [49].

Fig 3: Vaginal films

3. Vaginal Creams

Vaginal creams are used to deliver the antifungal, antibacterial and contraceptive drugs topically. Vaginal creams are messy to apply, uncomfortable and sometimes embarrassing when they leak into the underclothing. Also, the exact dose is not provided because of the heterogeneous distribution of the formulation when applied into the vagina. But they are easy to use, formulate and are easily available. Premarin vaginal cream is indicated for the treatment of patients with refractory endometrial [50]. Conjugated equine estrogen vaginal cream can be used to relieve menopausal atrophic Vaginitis [51]. Bacterial vaginosis can be treated by clindamycin cream [52]. Dienoestrol cream may be useful in the symptomatic prevention of vaginal atrophy in postmenopausal women [53]. Postmenopousal vaginal atrophy can be treated with ovestin vaginal cream and estradiol vaginal cream [54, 55].

Fig 4: Vaginal creams

4. Vaginal Gels

The most widely used mucoadhesive vaginal drug delivery systems are gels [56]. In particular, for drugs designed for gynaecological use, a bioadhesive gels able to ensure prolonged contact between the active ingredient and the vaginal mucosa, and gradual release of that ingredient over time, provides the ideal solution in terms of efficacy and compliance by patients. Among vaginal formulations, gels are easy to manufacture, comfortable, and have the ability to spread onto the surface of mucous and to achieve an intimate contact with vaginal mucosa. Some of the marketed formulations of vaginal gels were shown in (Table 1) [57]. Moreover, because of their high water content and their rheological properties, they present the further advantage of a hydrating and lubricating action, which is particularly useful in pathological situations characterized by dryness of the vaginal mucosa. The employment of mucoadhesive polymers can improve the time of contact with the mucosa, delaying the loss of the formulation and prolonging the effect [44].

Fig 5: Vainal gel

Table 1: Marketed mucoadhesive vaginal gel [57]

Therapeutic drug(Brand name)	Intended use	Dosage form	comments	Company
Oxyquinoline sulphat, ricinolic acid, acetic acid (Acid jelly ®)	Maintenance of vaginal acidity, antiseptic	Vaginal gel	Maintain the pH 3.9-4.1	Hope Pharmaceutical
Nonoxynol-9 (Advantages ®)	Contraceptive	Vaginal gel	Bioadhesive in nature	Columbia laboratories
Etonogestrol, ethinyl estradiol (Nuva ring ®)	Contraceptive	Vaginal gel	Commonly reported adverse events are vaginitis, weight gain	Organon
Nonoxynol-9 (Conceptrol®)	Contraceptive	Vaginal gel	-	Advance Care Product
Progesterone	Infertility, secondary	Vaginal gel	Possible side effect	Fleet Laboratories

5. Vaginal suppositories and pessaries

Pessaries are solid, single dose preparations. They have various shapes, usually ovoid, with a volume and consistency suitable for insertion in to the vagina. They contain one or more active substances dispersed or dissolved in a suitable bases that may be soluble or dispersible in water or may melt at body temperature. Excipients such as diluents, adsorbents, surface activeagents, lubricants, antimicrobial preservatives and colouring matter, authorized by the competent authority, may be added, if necessary.

Suppositories can be easily applied to the vagina. Hydrated bioadhesive vaginal suppository formulations are formed of one or more hydrophilic polymers, such as sodium carboxymethyl cellulose, polyacrylic acids or polyacrylates, a pessary or suppository base, water (30 % by weight of the formulation) and an active ingredient. Vaginal suppositories or Pessaries weigh about 3-5gm and are molded in globular or oviform shape or compressed on a tablet press into conical shapes. Pessaries are a type of suppository intended for vaginal use. The larger size moulds are usually used in the preparation of pessaries such as 4g and 8g moulds. Pessaries are used almost exclusively for local medication, the exception being prostaglandin pessaries that do exert a systemic effect [58].

Fig 6: Vaginal suppositories and pessaries

Recent advances in vaginal drug delivery system

In bio adhesive drug delivery system, bio adhesive molecules capable of delivering the active compound for an extended period at a predictable rate are incorporated into a formulation. The vagina is a most suitable site for bio adhesive formulations as the product absorbs moisture, becomes a gel and releases medication in a time-controlled manner. Bioadhesive polymers that have been used for vaginal

formulation include HPC, polycarbophil and polyacrylic acid.
A bioadhesive polycarbophil gel, Replens R, is the available form in the market, which is used to retain moisture and lubricate the vagina. The formulation remains in the vagina for 2–3 days and maintains the vagina at healthy, acidic pH. Various peptide and protein drugs have also been administered via bioadhesive micro particulate vaginal delivery system. Hyaluronic acid based intravaginal delivery of calcitonin, a polypeptide used in the treatment of postmenopausal osteoporosis, have been a success for intravaginal administration of drugs for systemic effect.
In a recent study a new mucoadhesive vaginal dosage form for the antimycotic agent, clotrimazole, was developed by incorporating bioadhesive polymers viz. polycarbophyl, HPMC and Hyaluronic sodium salt into suppositories made of semi synthetic solid triglycerides. These polymers hold the suppositories in the vaginal tract for a longer period of time without adverse effects, thereby prolonging the residence of the drug on the vaginal epithelium. The presence of these polymers largely modulated the behaviour of suppositories in terms of adhesive force, liquefaction time and residence of the drug in the application site [59].

1. Solid polymeric carriers [60]
These are the specifically designed non-messy intravaginal drug delivery systems that can be used to generate a variety of controlled delivery profiles over periods ranging from several days to several months. These are of two types as follows:

Solid Hydrogels
Hydrogels are three dimensional hydrophilic polymer networks which can absorb huge amounts of water and other biological fluids. The networks consist of homopolymers or copolymers and they are insoluble because of physical crosslinks like crystallites or entanglements and chemical cross links such as junctions and tie points. Hydrogels possess thermodynamic compatibility with water due to which they swell in aqueous media. They act as carriers in swellable or swelling controlled release devices or regulates drug release in controlled release systems.
Hydrogels are a stimuli-sensitive and enviro-intelligent system that controls the drug release according to the temperature, pH, electrical field, ionic strength and specific analyte concentrations. Hydrogels as delivery systems can be promising when they are combined with the molecular imprinting technology. The gelation and retention of in-situ gelling vaginal formulations could be a landmark in improving the therapeutic efficacy of drugs. The phase change polymers polyoxypropylene and polyoxyethylene are used to form thermo reversible gels when incorporated into aqueous solution. Phase change polymers like 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.
Formulations based on a thermoplastic graft copolymer have been developed to provide the prolonged release of active ingredients like nonoxynol, progestins, estrogens, peptides and proteins in a vaginal environment. 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 the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and retention owing to the formation of a mucoadhesive gel [61].

2. Elastomeric Intravaginal Rings (IVR)[62]
The vaginal ring is an innovative platform for the convenient delivery of hormonal agents. The vaginal ring is a torous or circular shaped device which is made up of silicone elastomers which owing to its elastomeric properties exert a slight tension on vaginal walls. The factors governing the release rate from the ring are its design, solubility of drug in the elastomers and the molecular weight of the drug. For example: Very high release rates can be attained by using a high drug load at the ring surface whereas Moderate release rates may be attained by coating a homogeneous ring and If an even lower release rate is desired, the drug may be confined to a small diameter at the centre of the ring (core ring).
This innovative technology has the capacity to deliver a constant dose of drug intravaginally over an extended period of time in a single application, to deliver drugs such as medroxyprogesterone acetate, chlormadinone acetate, norethindrone, norgestrel, levonorgestrel to treat conditions such as eating disorders, depression, migraine headache, pain, obsessive compulsive disorders PMDD. Advantages of vaginal rings include its user controlled nature, do not interfere with coitus, does not require a daily intake of pills and allows continuous delivery of low dose steroids. They are approximately 5.5 cm diameter with a circular cross section diameter of 4–9 mm and the ring is inserted in the vagina.
The vaginal rings are of three types:

1. Matrix Type IVR
It is the simplest IVR device, manufactured by a single injection of an active elastomers mix that contains the drug homogenously dispersed throughout the polymer matrix.Drug release from these types of devices follow the typical First order pattern.

2. Reservoir Type IVR
In the reservoir or core IVR, the drug is located within a centralised core that is surrounded by a drug free silicone sheath that acts as a rate controlling membrane for drug diffusion. One of the main advantages of this type over matrix type is that the release characteristics can be readily modified, either by changing the thickness of the sheath layer or by varying the core length.
Reservoir rings are manufactured in following steps:

- A drug loaded core is first prepared either by injection moulding (for low drug conc. $\leq$ 30%) or by Extrusion (high drug conc., 30- 70%) of drug elastomers mix.
- The full cores may be cut into smaller core lengths depending on the required release rate.
- The cores are then encapsulated within silicone elastomers in two stages to produce the full reservoir ring.

3. Sandwich (shell) IVR
It is a reservoir type IVR and consists of a narrow drug containing layer located a fraction of millimetre below the outer surface of the ring and positioned between a

nonmedicated impervious central core and a non medicated outer rate controlling band. The position of the drug core close to the surface ensures that this is the best suited to the delivery of drugs having poor polymer diffusion characteristics. Nuva Ring is the only combined contraceptive vaginal ring available in the US market. It is a flexible, transparent, contraceptive vaginal ring consists of two active components, etonogestrel and ethinyl estradiol.

The ring releases 120 mg/day of etonogestrel and 15 mg/day of ethinyl estradiol over a 3-week period of use. Clinical trials show that Nuva Ring is an effective contraceptive ring with good cycle control and user acceptability. FemringR and EstringR are estrogen releasing rings used for estrogen therapy. FemringR, which is made up of silicone elastomers, contains acetate derived of estradiol (hydrolysed to estradiol after insertion), which is placed in the vagina once every trimester. Estring R is made of silicone polymers and when inserted in the vagina releases 7.5 mg of estradiol per day.

Vaginal Rings [63]

The vaginal ring technology offers an innovative platform for a convenient delivery of hormonal agents [64]. The vaginal ring is a small, flexible ring that has to be put into the vagina once a month to prevent pregnancy. The ring is easy to put in and one size fits most women. The ring contains hormones called estrogen and progestin. These are the same hormones that are in most birth control pills. If always used correctly, less than 1 out of 100 women will get pregnant each year using the ring. If not always used correctly, 8 out of 100 women will get pregnant each year using the ring. When it is used for first time, it takes several days to begin working. For the first seven days an adhesion contraceptive method is used. The hormones in the vaginal ring keep the ovaries from releasing eggs and thicken the cervical mucus to block sperm from getting into the uterus. The ring is inserted into the vagina. The ring stays in place for three weeks straight. It can be taken out the fourth week for menstruation. After the week off, simply a new ring is inserted and starts the cycle again.

Fig 7: Vaginal Rings

Benefits of using the vaginal ring

- The vaginal ring is safe, convenient, and very effective.
- Many women who use the ring have lighter, shorter, and more regular periods.
- Most women can get pregnant quickly after they stop using the ring.
- The hormones in the ring offer health benefits. The ring can offer some protection against acne, non-cancerous breast growths, ectopic pregnancy, endometrial and ovarian cancers, iron deficiency anemia, ovarian cysts, pelvic inflammatory disease, PMS symptoms, and menstrually-related migraine headaches.

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 [65].

***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 [66]. 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 [67]. The bioadhesive strength of the vaginal formulation can be measured by various techniques [68].

In vivo studies are conducted in different animal models to assess efficacy, distribution, spreading and retention of formulations in the vagina [69]. Gamma scintigraphy and colposcopy [70] 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 [71].

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 [72]. 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 [73].

Application of vaginal drug delivery system [74]

1. This route of drug administration is useful for vaginal immunization.
2. Multi-cycle administration of vaginal contraceptive rings.
3. Effective route for the treatment of local fungal infection such as Candidiasis.
4. Effective for the delivery of hormones.
5. Treatment or Prevention of STDs.
6. Delivery of peptides such as calcitonin for prevention of Osteoporosis.

Conclusion

The vaginal route act as a potential route for the delivery of therapeutically important molecules, such as microbicides and novel vaginal drug delivery systems includes vaginal tablets, vaginal films, vaginal creams, vaginal gels, Suppositories or Pessaries. These novel systems would enhance the delivery of many drugs offering better therapeutic outcomes. 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. From this review it was evident that the vaginal drug delivery is a promising area for continued research on the delivery of microbicides that can prevent HIV infection and other transmission of sexually transmitted diseases.

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