A REVIEW ON VAGINAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Some drugs are poorly absorbed after the oral administration. Over the last twenty years, extensive efforts have been made towards the administration of poorly absorbed drugs through different delivery systems and routes but the presence of a mucus laden cervix (vagina) in women provides an opportunity as a conjoint site for such drug delivery. The vaginal route has been rediscovered as a potential route for systemic delivery of various therapeutically important drugs avoid first pass metabolism. However, fruitful delivery of drugs through the vagina remains a challenge because of poor absorption of some drugs across vaginal epithelium. The various factors like vaginal physiology, age of patient, menstrual cycle are affecting the rate of drug absorption after vaginal administration. The future of vaginal drug delivery lies in the bioadhesive tablets, liposomes, niosomes and microparticles, which although relatively new and show great promise in providing truly controlled delivery of drugs. In the current study, further attention has been made on various polymers which are used in hydrogel which provide bioadhesive property to the vaginal formulations, so that the formulation remains vaginal tissues for proper time. The main objective of the present review is to summarize various vaginal drug delivery systems with an special emphasis an vaginal physiology, factors affecting the vaginal drug absorption, mechanism of vaginal epithelium drug absorption including the advances in the current approaches in vaginal drug delivery systems.

Keywords: Vagina, Bioadhesive, Microparticles.
INTRODUCTION

Vaginal drug delivery systems are traditionally used to deliver contraceptive and drugs to treat the vaginal infections. However, vaginal drug delivery is not limited to these drugs as the vagina has promise as a site to topically deliver drugs which will be absorbed systemically because of the dense network of blood vessels in the vaginal wall [1]. A formulation given by this route as pessaries, vaginal tablets, inserts, cream, powders, douches, gel, etc. The first truly controlled drug delivery systems for use in the vagina were developed in 1970, when the first vaginal ring was used for delivery of medroxyprogesterone acetate for contraception. Still, tablets, creams and counter (OTC) vaginal medications while vaginal rings are the most common long-term drug delivery systems currently used. In recent years vaginal Bioadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases [2]. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for an extended period of time including day hours and night, thereby enabling lower dosing frequencies. The concept of controlled-release drug delivery has also been successfully applied to the intra-vaginal administration of a systemic prostaglandin derivative for abortion indication. Intra-vaginal controlled-release drug delivery system is an effective means of continuing delivery of therapeutically active agents such as contraceptive steroids and prostaglandins.

Advantages of Vaginal Drug Delivery System

This route is the most preferred and targeted goal of new drugs and dosage forms, vaginal administration can be used as an alternative route in certain cases of therapeutic importance: In cases of nausea and vomiting, the act of taking medication orally may induce emesis so that the drug is vomiting before it is absorbed. Irritation to the stomach and small intestine associated with certain drugs can be avoided. Hepatic first pass elimination of high clearance drugs may be avoided partially [2]. Contact with digestive fluid is avoided, thereby preventing enzymatic degradation of some drugs. Drug delivery can be stopped by removing the dosage form e.g. Vaginal rings. Drugs which traditionally are only given parental may be administered vaginally either as such or in combination with absorption-promoting additives. Rapid drug absorption and quick onset of action can be achieved. Convenient for the patients, especially for those on long
term therapy, when compared with parenteral medication. The vaginal bioavailability of smaller drug molecules is good. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach. Self-medication is possible [3].

Classification of Intra-Vaginal Drug Delivery System [2, 4, 5]

- Vaginal rings
- Vaginal Tablet
- Vaginal Powder
- Vaginal Capsule
- Vaginal Ointment
- Vaginal gel and creams
- Suppositories

Vaginal Rings

Vaginal rings are circular ring type drug delivery devices designed to release the drug in a controlled fashion after insertion into the vagina. Advantages of vaginal rings are that it is user controlled, does not interfere with activity, does not require a daily intake of pills and allows continuous delivery of low dose steroids. They are approximately 5.5 cm in diameter with a circular cross section diameter of 4–9 mm and the ring is inserted in the vagina. In simple vaginal rings, drug is homogeneously dispersed within a polymeric ring [6]. Drug at the surface of the ring is released faster than drug in the inner layer of the ring. Sometimes, drugs in the outermost layer provide an initial burst release. To obtain a constant release of drug from vaginal ring, sandwich or reservoir type rings has been developed. Sandwich type devices consist of a narrow drug containing layer located below the surface of the ring and positioned between a non-medicated central core and a no medicated outer band. In reservoir type rings, drugs are dispersed in a centralized core, which is then encapsulated by a drug free layer of polymer. In a single ring, it is possible to have several cores of different drugs and thereby allowing administration of several drugs from the same device [7]. The rate of drug release can be modified by changing the core diameter or thickness of the no medicated coating. The material for making vaginal ring is usually polymeric in nature. Much of the vaginal ring literature relates to commonly used polymer, poly (dimethylsiloxane) or silicone devices, although other elastomeric polymers such as ethylene vinyl acetate and styrene butadiene block copolymer have been tested in recent years. Ethylene vinyl acetate polymers are classified by the content of vinyl acetate. The addition of vinyl acetate units in the polyethylene provides the following advantages: increased flexibility, improved
optical properties, greater adhesion, and increased impact and puncture resistance.

![Image of Nuva Ring Compressed](image)

**Figure 1: Nuva Ring Compressed**

Further, the clinical acceptability of rings made of ethylene vinyl acetate is very high. In evaluating the tolerability of ethylene vinyl acetate no medicated vaginal ring of diameter 54 mm, the acceptability percent among the subjects involved in the study was 91%. The ring was to remain inserted for 21 consecutive days after insertion, permitting temporary removal during coition. Most of the women judged the ring easier to insert and remove. No adverse effects were experienced among the test group during the study period. Vaginal rings are used for contraceptive and hormone replacement therapy. For most contraceptive applications, the rings are placed in the vagina for 21 days followed by a week of ring free period. Nuva Ring is the only combined contraceptive vaginal ring available in the US market. Nuva Ring is a flexible, transparent, contraceptive vaginal ring containing 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 elastomer, contains acetate derived of estradiol, which is placed in the vagina once every trimester. Estradiol acetate is hydrolyzed to estradiol after being released from the delivery device. Estring R is made of silicone polymers and when inserted in the vagina releases 7.5 mg of estradiol per day [5].
Vaginal Tablet

Tablet for vaginal delivery is manufactured either by wet granulation or direct compression.

![Image of Vaginal Tablet](image1.png)

Figure 2: Vaginal Tablet

Table 1: Components

<table>
<thead>
<tr>
<th>Components</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose</td>
<td>Diluent</td>
</tr>
<tr>
<td>Anhydrous lactose</td>
<td>Diluent</td>
</tr>
<tr>
<td>Crossarmellose</td>
<td>Binding agent</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Lubricant</td>
</tr>
</tbody>
</table>

Vaginal Powder

Vaginal powder is prepared by dissolving hydroxypropyl cellulose in water with heat. The mixture is slightly cooled and the bisphosphonate is added. The mixture is lyophilized.

Vaginal Capsule

Vaginal capsule is prepared by filling the prepared powder into capsules. While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and additions may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

Vaginal Ointment

Vaginal ointment according to the invention comprises an oil and an aqueous phase. For preparation of the ointment the drug selected from the group of compounds consisting of alendronate, clodronate, tiludronate, pamidronate, etidronate, ibandronate, neridronate, residronate, zoledronate or olpadronate is dissolved in the aqueous phase.
and the oil phase added. Both phases are properly mixed [8].

**Vaginal Creams and Gels**

Creams and gels are used for topical delivery of contraceptives and anti-bacterial drugs. These vaginal dosage forms are messy to apply, uncomfortable and sometimes embarrassing when they leak into the undergarments. Further, creams and gels may not provide an exact dose because of nonuniform distribution and leakage. The desirable properties of vaginally administered cream or gel against microbicides are acceptability and feasibility. They must be easy to use, non-toxic and non irritating to the mucus membrane. In the treatment of bacterial vaginosis, metronidazole and clindamycin vaginal cream are found to be nearly as effective as orally administered drugs. To evaluate the efficacy of an antibacterial vaginal cream in the treatment of bacterial vaginosis, Lamont et al. Carried out a randomized, placebo controlled 3-day course study during the second trimester of pregnant women. They found that the clindamycin vaginal cream was well tolerated and more efficacious than placebo in the treatment. In the absence of an effective prophylactic anti-HIV vaccine or therapy, current efforts are aimed at developing topical intravaginal formulations of anti-HIV agents or microbicides to reduce the mucosal and perinatal virus transmission. Vaginal creams and gels could be based on the principle of emulsion or hydrogel based drug delivery. During the past few years, considerable work has been done on the development of hydrogel controlled release drug delivery systems. These hydrogels, when placed in an aqueous environment, swell and retain large volumes of water in their swollen structure and release drug in a controlled fashion. A swelling controlled release hydrogel delivery system for intravaginal administration of an antifungal drug, miconazole, has been reported. Hydrogels are hydrophilic polymers that have been cross-linked by means of covalent bonds. A 3% alginate gel of nonoxynol-9 has been investigated for intravaginal spermicide delivery. In the study, it was shown that spermicidal activity and diffusion of the agent changes with the pH and osmolarity of the formulation. Recently, gel-microemulsions have been proposed as a nontoxic vaginal formulation. A gel microemulsion based formulation of a spermicide with anti- HIV effect, a vinyl phosphate derivative of zidovudine, has been developed. Multiple intravaginal application of this drug as microemulsion gel formulation did not cause any damage in the vaginal epithelium in a rabbit model. The vaginal gel
has also been used for intravaginal vaccine delivery. Intravaginal delivery of cholera vaccine showed a greater mucous response in the female genital tract compared to oral administration of the vaccine. Antibacterial agents and drugs for cervical ripening and induction of labor are also available as a vaginal gel form. Oxytocin, dinoprostone and misoprostol are commonly used drugs for cervical ripening and induction of labor. Recently [9] studied the efficacy of dinoprostone (prostaglandin E2) vaginal gel versus vaginal tablet in the induction of labor. Their retrospective analysis was performed to compare the labor outcomes between women who received dinoprostone vaginal gel (1–2 mg) over a 3-month period and women who were receiving a dinoprostone vaginal tablet (3 mg) over the following 3 months. The authors observed no statistically significant differences in labor outcomes between dinoprostone vaginal gel and tablet used in the induction of labor. However, in their analysis, the authors did not compare the safety between the two dosage forms. In another similar study, the efficacy and safety of dinoprostone vaginal insert with vaginal tablet was compared. Women who were requiring labor induction were randomly assigned to receive either a 10 mg dinoprostone vaginal insert or 3 mg dinoprostone tablet twice at six-hour intervals. The complications for the two dosage forms were tested by the occurrence of uterine hyper stimulation, abnormal fetal heart rate patterns, use of h-2 adrenergic drugs and fetal outcome. The interval from insertion of the induction agent to the onset of regular uterine contractions was similar between the two groups. In seven of eight patients from the group who were receiving the insert and experienced uterine hyper stimulation, removal of the insert was sufficient to stop the hyper stimulation. However, in the group that was receiving tablet, eight out of nine subjects needed medical intervention to end hyper stimulation. An interesting study by [10] comparing the efficacy of vaginal misoprostol and dinoprostone vaginal gel for labor induction. The principal outcome measures were oxytocin requirement in labor, the necessity of analgesia, mode of delivery, time for induction to delivery and neonatal outcome. In misoprostol administered group, a reduced need for oxytocin in labor, but a highly significant reduction in time for induction to delivery was observed compared to the dinoprostone administered group. However, no differences in the requirement of analgesia, mode of delivery, or neonatal outcome were noticed between the two cohorts. In another
recent randomized controlled study involving dinoprostone suppository, the vaginal misoprostol administration was found to be more efficacious than prostaglandin F2-a gel and dinoprostone suppository.

Nevertheless, compared to PGF2-a gel, both misoprostol and dinoprostone suppositories showed a reduced need for oxytocin and shorter labor duration. Since the inception of misoprostol in 1993 for labor induction, the intravaginal administration of this drug has been studied extensively. Recently, there have been several citations in the literature comparing the effectiveness of oral versus vaginal misoprostol delivery. The dose required for the oral delivery of misoprostol is usually 4 times than that of intravaginal dose. However, there have been few conflicting reports too with respect to the efficacy of the route of misoprostol administration. For example, Hall et al. reported that oral misoprostol had the potential to induce labor as safely and effectively as that produced by vaginal misoprostol, whereas a study by [11] found that vaginal administration of the drug was more efficacious than the oral route although the oral (100 mg) and vaginal dose (25 mg) as well as the intervals of drug administration were the same in both these studies, the results were not similar. This disparity in their observation could be attributed to their principal outcome criterion, which was assessed in each of these studies. In the former study, the key outcome measurement was the time for the start of induction to vaginal delivery, while in the latter study the chief outcome measurement was the number of women who went on to deliver vaginally within 24h of initiation of the first dose of misoprostol. In a specific study evaluating the safety and efficacy of oral versus vaginal misoprostol administration, the investigators
found that, although oral misoprostol had similar effects as the vaginal form, the oral administration was associated with higher frequency of high uterine contractility and intervention. In an interesting report, concerning the sublingual use of misoprostol in first-trimester surgical abortion, the authors found that sublingual delivery of misoprostol was an effective alternative to vaginal administration for cervical priming. Although a greater incidence of side effects was observed, the patient acceptability was quite high. From an analysis of different studies performed employing the oral and vaginal routes of misoprostol administration, it appears that the current recommended vaginal misoprostol dose (25 Ag) is efficacious and safer than the 100 Ag oral doses. Also, as rightly noticed by [12] different methods of misoprostol administration may not be equivalent with regard to efficacy and safety.

**Suppositories**

A large number of vaginal medications are available in the form of tablets or suppositories. Some authors use the terms pessaries and suppositories interchangeably and consider vaginal tablets as a separate dosage form. These vaginal formulations are designed to melt in the vaginal cavity and release the drug for several hours. Suppository systems are now most commonly used to administer drugs for cervical ripening prior to childbirth and local delivery of drugs. Drugs that are administered as suppository include dehydroepiandrosterone sulfate for ripening effect on the uterine cervix, Miconazole for vaginal candidiasis and progesterone for hormone replacement therapy. Vaginal tablets may contain binders, disintegrant and other excipients that are used to prepare conventional oral tablets. It has the advantage of easy of manufacture and insertion. Mucoadhesive polymers are sometimes used in vaginal tablet formulation to increase vaginal residence time. Drugs that are administered as vaginal tablets include itraconazole, clotrimazole and prostaglandins. Presence of hydrophobic and release retarding materials may decrease the absorption of a drug from a vaginal formulation. Too hydrophobic drugs may not be suitable for vaginal tablets. Presence of penetration enhancers such as surfactants, bile salts can significantly enhance absorption.
bioadhesive drug delivery systems

Conventional vaginal formulations are associated with disadvantages of low retention to the vaginal epithelium, leakage and messiness thereby causing inconvenience to the user. To circumvent these problems, bioadhesive drug delivery systems are being propagated. Bioadhesive polymers that have been used for vaginal formulation include polycarbophil, hydroxypropylcellulose and polyacrylic acid. A bioadhesive polycarbohil gel, ReplensR, is available 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 attempts to administer via bioadhesive microparticulate vaginal delivery system. Hyaluronic acid based intravaginal delivery of calcitonin, a polypeptide used in the treatment of postmenopausal osteoporosis, have shown promise for intravaginal administration of drugs for systemic effect. A mucoadhesive controlled release drug delivery system for nonoxynol-9, a spermicidal agent, has been reported. This gel type system consisting of varying levels of nonoxynol-9 and EDTA, a chelating agent, were formulated using car-pool 934P polymer. The car-pool 934P polymer system provided a high burst release of nonoxynol-9 in the first 2 min and controlled release for 6 h. Gel type dosage form has the advantage over the tablet type dosage form, in that the former has greater surface contact and less irritation. In one study a new mucoadhesive vaginal dosage form for the antymycotic agent, clotrimazole, was developed by incorporating bioadhesive polymers viz. polycarbophil, hydroxypropylmethylcellulose 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 permanence of the drug on the vaginal epithelium. The presence of mucoadhesive polymers largely modulated the behavior of suppositories in terms of adhesive force, liquefaction time and permanence of the drug in the simulated application site; however, their presence did not alter the release of the drug. The developed formulations showed good technological and adhesion properties and the ability to hold the dosage form at the application site. Assemblies for in vitro measurement of Bioadhesive strength and retention characteristics of a polymer in a vaginal delivery system have been reported. A modified simulated vaginal fluid was used in...
bioadhesion. Isolated lamb vaginal epithelium and cellophane saturated with simulated vaginal fluid were used a model membrane. The principle of bioadhesion is based on the measurement of tensile strength or shear stress required to break the adhesive bond between a model membrane and test formulation. The delivery system is placed between two model membranes fixed on flexible supports in the assemblies for a certain period of time. After the adhesive bond is formed, the force required to separate the bond is measured and calculated as bioadhesive strength. Such assemblies are useful for comparative evaluation of various polymers for bioadhesion and retention properties in-vitro.

Evaluation

Evaluation of Bioadhesive Tablets

The formulated tablets (10 in number) of each batch were evaluated for hardness using the Monsanto hardness tester (Tab Machines, India). Friability was determined according to the procedure mentioned in USP. Mass variation of the formulated tablets (20 in number) was tested in accordance with the procedures given in Indian Pharmacopoeia. The swelling rate of bioadhesive tablets was evaluated by using a 1% agar gel plate at 37°C [13, 14, 15].

In Situ Bioadhesive Strength

Bioadhesive strength of the tablets was measured by a method reported by [16]. Porcine vaginal mucosa was used as a model membrane and acetate buffer, pH 6.0 as moistening fluid for measurement of bioadhesive strength. The surface of the mucosal membrane was first blotted with a filter paper and then moistened with acetate buffer. The force required to detach the tablet from the mucosal surface was taken as the measure of bioadhesive strength. The thickness of the vaginal mucosal membrane was 0.01–0.05 mm and the temperature was maintained at 37°C throughout the study. Each experiment was performed using porcine vaginal mucosa obtained from three different animals. Vaginal mucosa was obtained within 1 hr of sacrificing female pigs at the local slaughter house. The age (mean ± SD) of female pigs was 1.5 ± 0.5 years.

Dissolution Rate

The in vitro dissolution studies were carried out using the USP type 5-paddle method. The dissolution medium contained a 65:35 ratio of 0.1 mmol L–1 acetate buffer pH 6.0 and dioxane. The medium was maintained at 37 ± 1 °C and was stirred at 100 rpm. Samples (3 ml) withdrawn at suitable time intervals were compensated with fresh dissolution medium
and assayed spectrophotometrically at 270 nm. It was made clear that none of the ingredients used in the matrix formulation interfered with the assay. Each experiment was performed in triplicate.

**Stability Studies**

The selected formulation containing a CP/sodium alginate 2:1 ratio (batch C3) was subjected to accelerated storage conditions (40 ± 2 °C/75 ± 5% RH for 6 months). The formulation was analyzed for organoleptic characteristics, hardness and dissolution. Similarity factor f2 was calculated to compare the dissolution profiles according to equation

\[
f_2 = 50 \log \left[1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right] \times 100
\]

\(T_t\) and \(R_t\) are the percent drug dissolved at each time point for test and reference. Three tablets were subjected to this study.

**Selection of Model Mucosa**

Several types of mucous have been used as model biological tissues for the evaluation of bioadhesion, which included rat intestine, pig oral, bovine sublingual, cow vaginal mucosa. In our study, the cow vaginal mucosa was preferred. Vaginal mucous removed from newly sacrificed cows was used as a biological matrix. It was stored at 30°C until bioadhesion studies. In bioadhesive studies, the samples were thawed and cut to a suitable size. Investigation of the bioadhesive strength of tablets was done with a tensile-tester apparatus (ZWICK D- 7900). For adaptation of the apparatus to the bioadhesive tablet test, two metallic supports were constructed. The lower one supports the tablet and the upper one for the vaginal mucosa. The lower one was mobile while the upper one was stationary. The tablet and mucosa were attached to the metallic clamps with a cyanoacrylate type glue. A sample of 10 ml of distilled water was placed on the tablet surface using a Hamilton syringe and two surfaces were brought into contact for 10 min to maintain a stronger contact between the tablet and the mucous. The descending speed of the lower support was set to 20 mm/min and the detachment test was carried out. All tests were done at room temperature [17].

**Recent Advances in Vaginal Drug Delivery System**

Vagina is an important site for the delivery of drugs, particularly contraceptives for ages. As the advancement in pharmaceutical technology, the new delivery systems are taking the place of the traditional delivery systems such as suppositories, tablets, creams.
and gels. The consideration of women’s opinions on vaginal products is also important for the development of acceptable dosage forms and better compliance. Mucoadhesive systems have a unique place among the different new delivery systems. Mucoadhesive polymers have been successfully applied for systemic and local vaginal drug delivery [18]. Acrylic acid polymers (Carbomer or polycarbophil) and cellulose derivatives, such as hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropyl methylcellulose have been widely used as mucoadhesive polymers for the preparation of mucoadhesive vaginal drug delivery systems. There are a number of patents based on both groups of polymers. In particular it can be said that polyacrylic acid polymers are excellent multipurpose vehicles for vaginal drug delivery [19]. The current systems are used for vaginal lubrication, contraception, vaginal infections, labour inducement and infertility. Among the possible topical compositions, gels present notable advantages in comparison with other types of pharmaceutical products, such as good compliance with administration by the patient and ease of distribution of the pharmaceutical product on the surface of the vaginal mucosa. Gels in particular, on account of the high water content in their structure, present the further advantage of a hydrating and lubricating action, which is particularly useful in pathological situations characterized by dryness of the vaginal mucosa. Despite the numerous vaginal gel formulations patented, relatively few gel preparations are commercially available. Most of them are used for contraception and moisturization of the vagina. Up to our knowledge, there are no commercially available mucoadhesive vaginal tablet formulations present. When present patents checked for mucoadhesive vaginal drug delivery systems it can be noticed that there are many patents available having these key words. Moreover, as it is a general complain, these patents claim several different things. For instance, some of them have many active and inactive ingredients with a broad range of quantity or one parent have a claim of even different dosage forms in the same application such as gel, ointment, tablet, film or suppository etc. For vaginal application. This claim obviously written just to increase the coverage of the patents to make breaking attempts of patently impossible. It is really difficult to find precise patents and precise claims. All claims were found to be exaggerated much. It is therefore difficult to focus on precise aim. It may be just normal for applicant to increase the
Vaginal drug delivery systems are currently limited to vaginal rings, pessaries, SUPPOSITORY, bioadhesive tablets, and some bioadhesive microparticulate systems. The ongoing trend of research work is on nanoparticles drug delivery systems in vaginal route. Recent research efforts have perused applications other than contraception and vaginal infections to use these delivery systems to treat cancer and to deliver various protein and peptide drugs. The potential exists for a much wider use of vaginal delivery systems than currently existing systems. Hopefully novel bioadhesive systems in regards to microparticulate and nonparticulate systems will be developed in an advanced manner to meet these opportunities.

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