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A Detailed Review on Novel Vaginal Drug Delivery Systems

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ABSTRACT

Traditional vaginal medication delivery methods include drawbacks such low bioadhesive characteristics, generate leakages, limited residence time in the genitourinary tract, and the vaginal tract's ability to self-clean itself. The creation of novel vaginal formulation technology is required to meet requirements such desired product dispersion throughout the vagina, retention for intended intervals, sufficient release of medications, and improvement of human reproductive health. The conventional medication delivery methods, such as pessaries, pills, creams, foams, irrigations, etc., are being replaced by the new vaginal drug administration systems as a result of advancements in pharmaceutical technology. Innovative drug-loaded inserts, hydro-gel systems containing phase change polymers like poloxamer exhibit sol-gel transition in response to body temperature, pH, and specific ions, liposomes, micro emulsion-based vaginal gel, vaginal rings, cubic gels, formulations based on polystyrene, and formulations based on silicone elastomers are some of the approaches used to develop recent vaginal drug delivery systems. The distribution of nanoparticulate drugs via the vaginal channel has become a new research trend. Unlike traditional methods of contraception and vaginal infections, novel approaches use applications other than those mentioned above. Vaginal delivery techniques have the potential to be utilised on a much larger scale than currently possible.

1. INTRODUCTION:

The scientific community and pharmaceutical industry are currently very interested in finding new ways to deliver medications that are poorly absorbed after being administered orally. Despite having the potential to be a non-invasive route of drug administration, it is clear from the number of scientific publications that have been published in pharmaceutical journals over the past 10 years that the human vagina is still a relatively unexplored route of drug delivery[1].

Traditionally, only medications that act locally, such as steroids, prostaglandins, spermicidal agents, antibacterial, antifungal, and antiviral medicines, could be used during vaginal birth. Due to its large surface area, strong vascularity, and permeability to a wide range of compounds including peptides and proteins, antigens, the prospect for systemic delivery through the vagina was eventually explored[4].

These drug delivery methods demonstrate that diffusion is the primary penetration mechanism for the majority of active compounds. While most hydrophobic compounds are absorbed primarily through intracellular pathways, hydrophilic substances are more preferentially -absorbed through pores found in the vaginal mucosa[5].The vagina is an ideal delivery route for both systemic and local therapies due to its extensive network of blood vessels. Although there are several advantages to vaginal drug delivery, such as the ability to avoid first-pass metabolism, ease of administration, and high permeability for low molecular weight drugs, other factors, such as gender specificity, individual sensitivities and beliefs regarding personal hygiene, local irritation, the impact of sexual activity, and variability in drug absorption based on epithelial thickness, have shown to be barriers to using this method[2].

The limitations of current available vaginal formulations, such as leaking, messiness, and short residence times, contribute to low subject or patient compliance. In an effort to meet both clinical and user requirements, novel vaginal drug delivery systems are being developed[4].

Drug distribution via this route has a number of disadvantages, including limited bioavailability, gender specificity, cultural sensitivity, personal hygiene, local irritability, influence of sexual behavior, and most importantly changes in physiological condition based on age[1].Despite all the benefits of a vaginal application, postmenopausal and menstrual cycle

changes to the membrane must be taken into consideration. In postmenopausal woman the reduced epithelial thickness may change the original absorption rates of drugs significantly[6].

For medications including bromocriptine, propranolol, oxytocin, calcitonin, LHRH agonists, human growth hormone, insulin, and steroids used in hormone replacement treatment or for contraception, this route offers a superior substitute to the parenteral route. Delivering hormonal contraceptives through the vagina is a great option[7]. Today, there is a great need to use different mucosal delivery methods to administer medications that are poorly absorbed after oral administration 1.The first truly controlled drug delivery system for use in the vagina was developed in 1970,when the first vaginal ring was used for delivery of medroxyprogesterone acetate for contraception[8].sometimes it has been noted that similar with other mucosal sites (such the mouth, nose, and rectum), the bioavailability of peptides delivered vaginally is often quite poor but can be enhanced by use of absorption enhancers. Bioadhesive microparticles and tablets have recently been the subject of research, and they hold a lot of potential as a controlled drug delivery system for vaginal applications for the treatment of both systemic and topical illnesses[9].Hydrogels and hydrophilic polymers have been applied to numerous vaginal applications. For this purpose, a variety of natural, synthetic, and semisynthetic polymers have also been explored[10].

However, due to some medications' limited absorption across the vaginal epithelium, effective drug delivery through the vagina continues to be difficult. The bioadhesive tablets, liposomes, noisome, and microparticles, albeit yet in their infancy, have great promise for enabling genuinely regulated drug delivery. They are the wave of the future for vaginal drug delivery[11].The vaginal cavity has a potential for noninvasive, controlled transmucosal delivery of both local and systemic therapeutically active compounds[12].

2. ANATOMY AND PHYSIOLOGY OF THE VAGINA:

In the pharmaceutical literature, human vagina is often described as slightly S-shaped fibromuscular structure between 6 and 12 cm long, with two distinct and differently oriented portions at a 130° angle from the uterine cervix[13]. 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 no secretory stratified squamous epithelium; its thickness 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 the tunica adventitia, areolar connective tissue and a large plexus of blood vessels[15-16]. Vaginal tissue does not contain fat cells, glands or hair follicles[17]. The surface area of the vagina is composed of numerous folds, which are often called Rugae[18] and is significantly increased by the presence of several rugae, and its elasticity is augmented by the smooth elastic fibers in the muscularis and the loose connective tissue of the tunica adventitia. There are no fat cells, glands, or hair follicles within the vagina, and all vaginal secretions are transudate in nature[15].

Venous drainage is complex and bypasses the hepatoportal system. The vaginal veins form venous plexuses along the sides of the vagina and within its mucosa and communicate with the vesical, uterine, and rectal venous plexuses and ultimately drain into the internal iliac. In addition, vaginal, uterine, vesical, and rectosigmoid veins from the middle and upper vagina drain directly in to the inferior vena cava[19]. The strong vascular connections between the vagina and uterus have led to the hypothesis that when hormones are delivered vaginally, a "first uterine pass effect" may occur[20].

The vagina's lymphatic drainage is interesting because of the several compartments that exist within it depending on the embryo. The upper two thirds of the vagina drain to the pelvic and para-aortic lymph nodes, whereas the lower third drains to the inguinal lymph nodes. Both somatic and visceral innervation exist in the vagina. Pudendal nerve provides primarily somatic innervation to the lower part, whereas inferior hypogastric and uterovaginal plexuses provide visceral innervation[21].

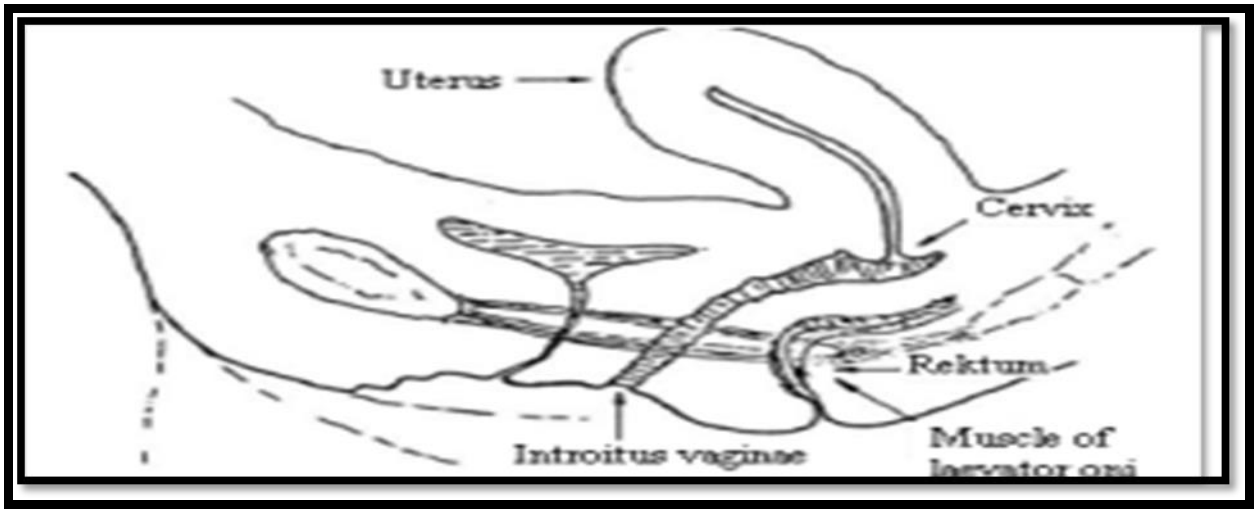


Figure 1: Graphical description of the vagina.

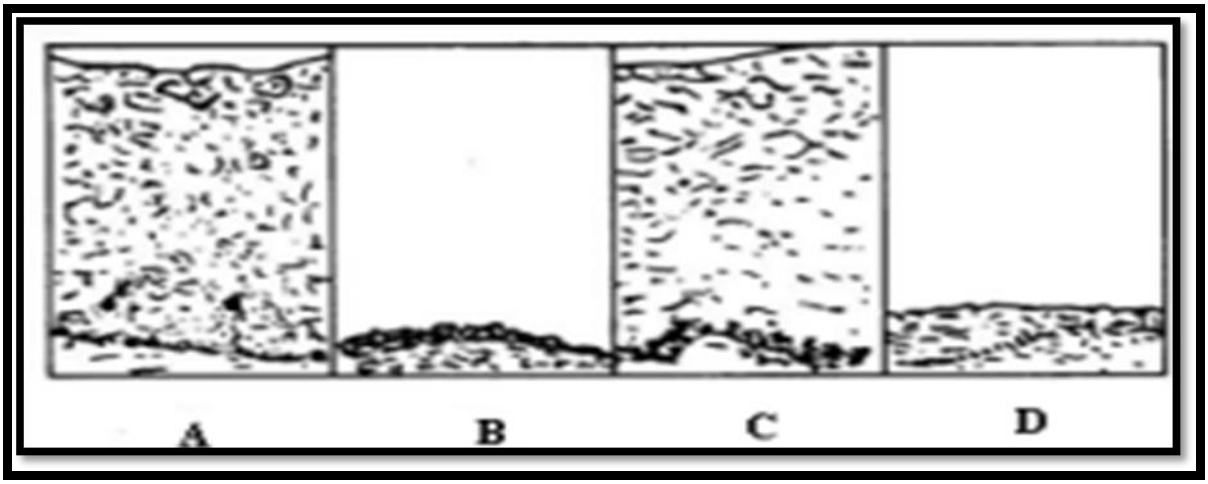


Figure 2: Comparison of epithelial thickness of the vaginal tissue

A-newborn, B-child, C-adult, D-menopause

The epithelial layer, the muscular coat, and the tunica advent are the three layers of the vaginal wall. The thickness of the vaginal epithelial cell layer changes by approximately 200–300 Am[18].

The vagina has an excellent elasticity because of the presence of smooth elastic fibers in the muscular coat. Loose connective tissue of tunica advent further increases the elasticity of this organ. A plexus of arteries extending from the internal iliac artery, uterine, middle rectal, and internal prudential arteries make form the network of blood vessels that give blood to the vagina. There are numerous arteries, blood vessels, and lymphatic vessels in the vaginal walls. Because blood from the vagina enters the peripheral circulation via a rich venous plexus, which empties predominantly into the internal iliac veins, drugs received via the vagina do not undergo first-pass metabolism[22].There is some drainage to the hemorrhoidal veins as well. The prudential nerve, the inferior hypogastria, and the uterovaginal plexuses all receives the lower region of the vagina with nerves. supply[21]. Although the vagina does not possess any gland, it secretes a large amount of fluid[16].Vaginal fluid is mostly composed of leucocytes and cervical secretion and transudation from the blood vessels[23].The endometrium and fallopian tubes also secrete substances that contribute to the vaginal fluid[16].Like the thickness of the vaginal epithelium, the amount and composition of the vaginal fluid also change throughout the menstrual cycle.

In contrast to postmenopausal women, who produce fluid at a rate of 50% less than that of reproductive-age women, fluid is produced by women of reproductive age at a rate of 3- 4 g/4

h. Fluid may contain enzymes, inhibitors of enzymes, proteins, carbohydrates, amino acids, alcohols, hydroxyl ketones, and aromatic compounds[24].

The vaginal wall is devoid of gland and is covered by a surface film of moisture, which is composed of mucous (about 2 gm of mucus per day, from the cervix) and the fluid exuded from vascular lamina pro prier. The vaginal fluid may also contain additional secretions from the uterus and from Bartholin's glands. With increase in age of women, the thick ness of vaginal epithelium and the amount and composition of the vaginal fluid changes[24]. The rate of vaginal fluid production is affected by the menstrual cycle and sexual arousal. The pH of the vagina is acidic which is maintained by the action of vaginal bacteria (*Lactobacillus acidophilus*) which converts glycogen from extol acted epithelial cells into lactic acid and the lactic acid acts as a buffer to maintain the vagina pH from 4 to 5. Menstrual blood, cervical and uterine secretions and also semen will act as an alkalinizing agent and increase the vaginal ph. The human vaginal fluid may contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl ketones and aromatic compounds[26]. The vagina has a dense network of arteries and veins that form a dense network which provides a rich blood supply and consequently the vagina is well suited for the *r*apid and steady uptake of hormones[27].

When vagina enters 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. Vagina is mainly consisting of two type of nerve supply. Among this one is peripheral, which primarily supply 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[3].

Due to this only woman 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[28]. The vascular supply of vagina constructed of extended arteries that cover the vagina from several sources. One of the major characteristics of vascularity of vaginal tissue that has attracted attention recently is the postulation of a fast uterine pass effect, or direct preferential vagina to uterus transport. A significantly administration can be taken as evidence for the above findings[14].

3. FACTORS AFFECTING THE VAGINAL ABSORPTION OF DRUGS

Absorption life-cycle:

Drug dissolution in the vaginal lumen and membrane penetration are the two key processes in the absorption of medications from vaginal delivery systems[29]. The absorption profile from vaginal drug delivery systems may be impacted by any biological or formulation factor that affects drug dissolution and membrane transport[30]. It is known that cyclic variations in the vaginal epithelium's thickness can affect how well drugs are absorbed. There are conflicting accounts in the literature about how the development of vaginal epithelium affects drug absorption. option with the increase in vaginal epithelium. While progesterone seems to be better absorbed from thicker, more vascularized epithelium, steroids and local estrogen seem to be better absorbed from postmenopausal epithelium that is thinner[17,29,31]. Drug absorption may also be affected by the microbial balance between lactobacilli as the dominating flora and other, mainly Gram-negative anaerobes. Similarly, drug release can be affected by the changes in vaginal fluid volume and composition, pH, and sexual arouse al, as can the presence of cervical mucus [32-33].

3.1. Physiological Factors

The major factors that affect vaginal physiology include cyclic changes ,age, hormonal balance, pregnancy, pH fluctuations, and microflora concentration, thickness and porosity of the epithelium and volume, viscosity , thickness of epithelium layer, concentration of several enzymes, and production of vaginal fluid and extent of vaginal discharge can potentially affect drug release from any intravaginal delivery system and also alter its rate of absorption.[34].For e.g. vaginal absorption of steroids is affected by the thickness of vaginal epithelium[35].

From vaginal and cervical cells mostly the vaginal fluid transudes[26], which mainly contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl-ketones and aromatic compounds[36]. In general Vagina maintains a pH between 3.8-4.8, which influence by frequency of coitus, presence of cervical mucus and the amount of vaginal transudate[25].Again changes in the pH of vagina will alter degree of ionization of weak electrolytic since many are weak electrolytes 13 and affect the release profile of pH sensitive drugs[37].Furthermore, a glycoprotein gel made from cervical mucus may be used to

deliver drugs cells mostly, it may also act as a permeability barrier for various drug candidates at the same time[33].

Drugs will be more easily absorbed through the vagina before puberty because the vaginal epithelium is relatively thin; however, following puberty, the thickness of the vaginal epithelium increases, which results in a decrease in drug absorption. Several research have been done on the medication absorption through the vagina during various phases of the menstrual cycle or pregnancy. For example: reduced vaginal absorption of penicillin in women during the follicular phase of the menstrual cycle and during the last few months of pregnancy was noticed. This is correlated with the presence of thickened vaginal epithelium during these periods.[22]For example, The thickness of the vaginal epithelium has an impact on how well steroids are absorbed through the vagina. Vidarabine has been shown to have a 5–100 times higher permeability coefficient during the early disastrous stage than during the estrus stage in guinea pigs. The epithelial thickness is therefore reduced by long-term estrogen therapy[29].This anomalous finding was explained by the fact that vagina vascularity increased with the increase in the absorption of progesterone. In vitro study has shown that pH of the media has an impact on the release of PGE2 from vaginal preparations. Any change in the vaginal pH may affect the release profiles of pH sensitive drugs from vaginal drug delivery systems[29,30]. A thin, atrophic, and vaginal epithelium in postmenopausal women may facilitate medication absorption through the vagina. Due to the reduced vascularity and glycogen content of the vaginal wall, which causes dryness, the vaginal pH can rise and absorption may be reduced[35].

3.2. Physicochemical properties of drug:

And on the other hand physicochemical properties of drugs like solubility, dissolution rate, pika, chemical structure, chemical stability, charge on the membrane surface, pore size molecular weight and lipophilicity, ionization and surface charge the absorption across the vaginal epithelium[38].Straight-chain aliphatic alcohols with longer chains as well as lipophilic (as opposed to hydrophilic) steroids like estrone and progesterone are better absorbed from the vagina (hydrocortisone)[38,9].In fact, data on the human vaginal permeability of drugs with different physicochemical properties is very limited hence much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption[39].Further the affinity and bindings of drug with other related component, introduced to prepare a dosages form is an important factor, which can affect both the mass transfer and bio-diffusion of

drugs. A study by Owen et al. shows that, diffusion of nonoxynol 9 into the cervical mucus was increased by decreasing the pH, whereas at low drug concentration mass diffusion transfer tend to decrease with increasing osmolarity and decrease with increase with increasing pH at the same osmolarity[40]. In consideration to permeability literature shows that lipophilic steroids like progesterone and estrone having better permeability than the hydrophilic one like hydrocortisone and testosterone[41].

3.3 Vaginal Secretions:

Vaginal discharge is made up of a variety of substances, including transudates via the epithelium, cervical mucus, exfoliating epithelial cells, leukocytes, endometrial fluids, and tubal fluids, even though there are no goblet cells in the vagina and hence it does not make mucin. Inorganic and organic salts, mucin, proteins, carbohydrates, urea, and fatty acids (lactic) are all found in the cervical mucus[42].

3.4 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. The pH is raised by the alkalizing effects of menstrual, cervical, and uterine fluids and semen[43] the vaginal Ph should be controlled for successful vaginal delivery of drugs.

3.5 Microflora

The factors which influence the ecology of the vagina are glycogen content of epithelial cells, glucose, hormonal levels, and trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. The most prevalent organism is lactobacillus in the vaginal environment together with many other facultative and obligate aerobes and anaerobes The human genital tract has lower enzymatic which results in less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract[42].

3.6 Cyclic changes

The changes in hormone levels (especially estrogens) during the menstrual cycle led to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions.[8] In achieving consistent drug delivery creates problem with the variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes[49].

3.7 Pharmacological factors:

Although vaginal estrogen therapy was supposed to result in increased vaginal epithelium thickness and a decrease in drug absorption, it was shown that the vaginal progesterone absorption was increased in estrogen deficient women who were getting vaginal oestrogen[31].

4. Absorption enhancement techniques in vaginal drug delivery system

Poorly water-soluble medications may be absorbed more readily due to the high volume of vaginal fluid; however, the same condition also causes the drug to be removed from the vaginal canal, which reduces the amount of drug that is absorbed[33].Improvement of vaginal absorption by using penetration enhancers e.g. PEG (poly ethylene glycol) Increased contact time between the dosage form and the vaginal membrane, the use of mucoadhesive polymers like Carbopol, increased vaginal blood flow, which raises the concentration gradient across the vaginal mucosa, and the use of pro-drugs increase drug permeability by altering the hydrophilicity or lipophilicity of the drug all contribute to improved vaginal absorption. The extent of flow and retention of the medicament within the vaginal cavity depends on the type of formulation. By use of a bioadhesive dosage form the lower vaginal residence time can be improved that results in prolonged contact with the absorbing surface, and hence, better drug absorption[22]. A physical model of the vaginal membrane as a transport barrier has been described [45].

5. DRUG ABSORPTION MECHANISM FROM THE VAGINA

Like other mucosal drug delivery routes drug transport across vaginal membrane may occur by a number of different mechanisms: (a) diffusion through the cell due to a concentration gradient (transcellular route) (b)intracellular route / vesicular or receptor mediated transport mechanism or (c) diffusion between cells through the tight junctions (intercellular route). There are various vaginal drug delivery systems such as suppositories, gels, creams, vaginal rings, bioadhesive delivery systems etc. Vaginal absorption of a therapeutic agent from a controlled release drug delivery system, such as medicated vaginal ring, should be visualized.[22]The process for the drug-dispersing vaginal ring includes the following steps: (a) dissolving the finely ground drug particles; (b) evenly dispersing the drug particles into the surrounding polymer structure; (c) diffusion through the polymer matrix to the device surface; (d) particles into and diffusion across vaginal secretion fluid (which is sandwiched between the ring surface and vaginal walls); (e) uptake and subsequent penetration of the

drug through the vaginal mucosa(f) trans port and distribution of the absorbed drug molecules by circulating blood and /lymph to a target tissue[46].

6. ROLE OF ENZYMES IN VAGINAL DRUG DELIVERY / Vaginal enzymes in different species

The basal and exterior cell layers of the vagina are where there is a lot of enzyme activity. The ß-glucuronidase, acid phosphatase, some glucuronidase, and DPNH diaphorase are present in the exterior cell layers. ß- Glucuronidase, succinic dehydrogenase, DPNH diaphorase, acid phosphatase, and - glucuronidase are all present in basal cell layers. Proteases are important inhibitors of peptide and protein medication absorption into the systemic circulation in addition to enzymes. [proteases are prominent barriers for the absorption of peptides and protein drugs into the systemic circulation.[47,48]According to a recent study, the trypsin-like activity in rat vaginal smears I during the proestrus stage. The vaginal epithelium contains a variety of exopeptidases and endopeptidases that digest the majority of proteins and peptides. as suggested by *Lee*.[49] Numerous investigations on enkephalin in rabbit vaginal epithelium showed the existence of at least three peptide enzymes, including amino peptidase, dipeptidyl peptidase, and dipeptidyl carboxypeptidase, which are essential for the digestion of end cephalin (aminopeptidase metabolizes the methionine and leucine while dipeptidyl carboxy peptidase metabolizes the D-ala-met-encephala line).[50]The enzyme activity in the rat, rabbit and human is significantly lower than that of sheep and guinea pig. Overall, the aminopeptidase activity in the above species exhibited in the following order, sheep> guinea pig>rabbit>human>rat[51].

The authors conclude that the rat and the rabbit could be used as potential model animals for vaginal enzymatic activity studies and for the determination of degradation of protein and peptide drugs in the evaginate highest concentration of these enzymes was in the vaginal extract (0.045 U/ml) of the rabbit. A specific study [51].

7. Vaginal drug delivery system

7.1. Creams and gels

7.2. Suppositories and vaginal tablets

7.3. Vaginal rings

7.4 Vaginal Films

7.5 Vaginal Powder

7.6 Vaginal Capsule

7.7 Vaginal Ointment

7.8 Hydrogels

7.1 Creams and gels:

Vaginal Creams and gels are mainly used for topical delivery of contraceptives and anti-bacterial drugs. However, these forms are limited by the fact that they can be messy to apply, are uncomfortable, and may leak on to clothes. However, they can be as effective as orally administered medication in the treatment of bacterial vaginosis [52]. The delivery of intravaginal vaccines[53], pharmaceuticals for cervical ripening and labor induction[54,55] and abortion-inducing agents are other medications that can be administered as a vaginal gel. Recent studies suggest that vaginal immunization may offer protection against HIV and chlamydia[56,57]. 1 administering intravaginal vaccinations [53] Others that can be used as a vaginal gel include drugs for cervical ripening, labor induction, and abortion-inducing agents[54,55]. Recent studies suggest that vaginal immunization may protect against chlamydia and HIV[56,57].

Metronidazole and clindamycin are the most commonly used vaginal cream for the treatment of bacterial vaginosis. The main underlying principle behind vaginal creams and gels is that of emulsion or hydrogel-based drug delivery. These hydrogels, when placed in an aqueous environment, swell and retain large volumes of water in their swollen structure and results in drug release in a controlled fashion. A swelling controlled release hydro gel delivery system for intravaginal administration of an antifungal drug, Miconazole has been reported. A gel micro emulsion-based formulation of a zidovudine vinyl phosphate derivative spermicidal with anti-HIV action has been created. Additionally, vaginal gel forms of medications for cervical ripening and labor induction are offered. The most often prescribed medications for cervical ripening and labor induction are oxytocin, inopportune, and misoprostol.[42]

Figure 3. vaginal gel

Figure 4. vaginal cream

Further, creams and gels may not provide an exact dose because of nonuniform distribution and leakage. 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.

Oxytocin, inopportune and misoprostol are commonly used drugs for cervical ripening and induction of labor. Recently, Shetty et al. Studied the efficacy of inopportune (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 inopportune vaginal gel (1–2 mg) over a 3- month period and women who were receiving an inopportune vaginal tablet (3 mg) over the following 3 months. The authors observed no statistically significant differences in labor outcomes between inopportune 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 inopportune vaginal insert with vaginal tablet was compared. Women who were requiring labor induction were randomly assigned to receive either a 10 mg inopportune vaginal insert or 3 mg inopportune tablet twice at six-hour intervals. The complications for the two dosage forms were tested by the 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 Danieline et al. Comparing the efficacy of vaginal misoprostol and inopportune 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 inopportune administered group. However, no significant differences in the requirement of analgesia, mode or delivery, or neonatal outcome were noticed between the two cohorts. [58] Marcus E Brewster et al. reported a mucoadhesive cyclodextrin-based cream formulation of itraconazole shows effective therapeutic action on vaginal candidiasis[59]. Recently a gel microemulsion based formulation of spermicide with anti-HIV effect of zidovudine has been developed [60]. literature shows that monocarpic hydrogel formulations possess potent microbicidal activity against HIV, HSV, *Chlamydia trachomatis* and *Neisseria gonorrhea*, which is less cytotoxic than nonoxynol-9[61,62]. Cellulose acetate phthalate (CAP) used the pharmaceutical industries as enteric coating agent but recent study focused that it having a potency to absorb and inactivate HIV-1, HSV and other STIs [63]. Further utilizing this ability of CAP, a potential anti-HIV vaginal gel formulation has been formulated that are under phase II clinical trials [64]. An Intravaginal vaccine delivery by means of vaginal gel is also reported, even intravaginal delivery of cholera vaccine showed a greater mucosal response in female genital tract compare to oral administration of the vaccine [53]. Further oxytocin, inopportune and misoprostol commonly used for cervical ripening and induction of labor are also available in vaginal gel form. A study by Shetty et al. on the efficacy of inopportune (prostaglandin E_2) vaginal gel versus vaginal tablet for the induction of labor shows significant difference in the labor outcomes between two dosage forms [65]. Several literatures show the comparison of effectiveness between oral versus vaginal administration of misoprostol. The dose require for oral delivery of misoprostol is usually 4 times more 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 administration misoprostol shows the same potentiality to induce labor and also safety and efficacy, as that of vaginal administration [66], where as a study by Shetty et al. shows that vaginal administration of drug was more efficacious than the oral route [55]. Recently Chang et al. conducted a study to determine the thermosensitive behavior of clotrimazole vaginal gel and found that thermosensitive gels are potential candidate for safe,

convenient and efficacious treatment for vaginal candidiasis and also shows mucoadhesive properties when prepared with mixture of poloxamers and polycarbophil[67].

7.2. Suppositories and vaginal tablets:

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. Vaginal tablets may contain binders, disintegrant and other excipients that are used to prepare conventional oral tablets. It has the advantage of ease 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[58].vaginal formulation also known as Pessaries are designed to melt in the vaginal cavity and release the drug for several hours. These are now most commonly used to administer drugs for cervical ripening prior to childbirth and local delivery of drugs. Other drugs that are administered as suppository include dehydroepiandrosterone sulphate for ripening effect on the uterine cervix, Miconazole for vaginal candidacies and progesterone for hormone replacement therapy. The medicated pessaries have recently been used for delivery of prostaglandin E2 (PGE2) for ripening of the cervix and induction of labor[42].

Figure 5: vaginal suppositories

METHOD OF PREPARATION:

TABLETS: -

- The vaginal tablets were prepared by direct compression and direct blending.
- The ingredients were weighed and passed through sieve no # 20 ASTM.
- The materials sieved was blended into double cone blender at 15 RPM.
- The blended materials were again sifted through #30 ASTM sieve.
- These shifted materials were again blended into the blender for 15 min at 15 RPM.
- The lubricant is sieved through save no #60 ASTM and added to above blended mixture and again blended at 15 RPM.
- The direct compression was done for the formation of the vaginal tablet.

Vaginal Tablets

Only one vaginal tablet has been investigated as a microbicide dosage form. Preneet polyherbal was originally formulated with purified ingredients from Neem (Azedarach indica) leaves, Sapindas mucinosis (pericarp of fruit), and Mentha citrate oil into a pessary delivery device for sperm tidal and contraceptive purposes. Later on, the formulation was investigated and proven to be effective against some sexually transmitted infections[69]. The polyherbal was further developed into a vaginal tablet. The formulation consisted of purified extracts of dried leaves of A. indica (Neem tree; 80 mg), along with purified saponins from S. mucinosis (40 mg), M. citrate oil (20 mg), and quinine hydrochloride (30 mg) with other inactive ingredients such as sodium lauryl sulfate, sodium bicarbonate, Carbopol 934P, ethyl cellulose 20 M, Starla, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and purified talc. In clinical trials, this product was shown to be safe for vaginal use for up to 6 months with minor adverse effects [70].

The Vaginal tablets are same in composition as conventional oral tablets but it has the advantage of ease of manufacture and insertion. The lactose-based progesterone tablet can be used to deliver drug up to 24 hours and also can treat a variety of progesterone deficiency conditions such as menstrual irregularities, functional bleeding, luteal phase defects, and infertility.[42]

Figure 6: Vaginal Tablets[70]

Recently Muhd Aftab Allam et al. reported the development of acid-buffering bioadhesive vaginal tablet for the treatment of genitourinary tract infection and was found that acid-buffering bioadhesive vaginal tablet produce better antimicrobial effect than some of the marketed intravaginal delivery system[67]. Literature shows that polystyrene sulfonate (PSS) is also shows superior antimicrobial activity against HIV and HSV, therefore it is formulated in the form of vaginal tablet, which will not immobilize sperm, not cytotoxic and did not inhibit normal vaginal flora, so as proved as potential delivery system[71]. Amal Eid-Kamel et al. reported a chitosan and sodium alginate based bioadhesive vaginal tablet of metronidazole[72]. Further Gurpreet Kaur et al. conducted a study on bioadhesive vaginal clotrimazole tablet and concludes that polymers like carbolpol-934P, sodium carboxymethyl cellulose and sodium alginate are good candidate in respect to bioadhesive vaginal tablet formulation[73].

7.3. Vaginal rings

Vaginal rings are circular drug delivery devices designed to release the drug in a controlled fashion after the ring's insertion into the vagina. These are an alternative route of drug delivery for systemic application. Vaginal rings were developed in 1966, initially as contraceptive devices, after the demonstration that hormones could diffuse through is plastic tubes or solid discs at a constant rate[74]. Since then, vaginal rings have been made from flexible polyciliate and then ethylene vinyl acetate copolymer. Contraceptive rings have been used for years, both to deliver progestogens alone or in combination with estroge[75,76.] Contraceptive rings do not act as a physical barrier to sperm but prevent pregnancy by hormonal mechanisms, either by suppressing ovulation or changing cervical mucus. These rings, unlike the cervical cap or diaphragm, do not need to be fitted or placed over the cervix. The ring is simply inserted into the vagina, in contact with the vaginal epithelium. Contraceptive hormones are absorbed through the vaginal epithelium into the systemic circulation. The best studied ring is the levonorgestrel ring developed by the World Health Organization[77.] However, as with other progestogen-only methods, progestogen-only vaginal

rings do not completely suppress ovulation and have been associated with variable bleeding patterns, which led to the development of combined rings because the estrogen component maintains the endometrium and prevents break through bleeding. Rings for other than contraceptive use have been evaluated for delivery of estrogen for postmenopausal hormone therapy[78].Vaginal administration of estradiol is more effective in increasing serum and endometrial levels than is the oral route[79]. String, made of silicone polymers, contains 2 mg of estradiol and delivers 7.5 mcg per day; each ring is used for up to 3 months. It is indicated for treating symptoms of postmenopausal urogenital atrophy. It has also been shown to lower vaginal pH in women with recurrent urinary tract infections, thereby reducing the risk of further recurrence[80]. Vaginal rings are also being evaluated as a treatment option for endometriosis using danazol [81].

Most of the vaginal microbicide products in clinical trials or in preclinical evaluations have been investigated for use as a single dose in a coitally dependent manner. Vaginal rings currently available in the US market as contraceptive products are being investigated as controlled-release products for vaginal microbicide application. These microbicide vaginal ring prod cuts would provide a long-term release of the drug which results in less frequent need for application and in the end improved patient compliance. The only clinical evaluations of ring-based microbicide products incorporate TMC 120 (dipivefrine), a potent nonnucleoside reverse-transcriptase inhibitor. A dipivefrine loaded silicone-based, reservoir-type intravaginal ring was developed with the addition of polymers to modify controlled release characteristics [82,83]. It is a circular rings type device internally fabricated with silicone rubber, designed to release drug in a controlled fashion after insertion into vagina (Fig-2). Vaginal ring has been used to deliver medroxyprogesterone acetate, chlormadinone acetate, norethindrone, norgestrel, levonorgestrel etc.[8,84,85]

Several advantages are associated with the use of vaginal rings namely controlled release, does not interfere with coitus, allows continuous delivery of low dose of drug and does not require daily intake of pills. The rings are approximately 6 cm in diameter and have circular cross-sections approximately 4-8 mm in diameter. Vaginal rings are used for contraceptive and hormone replacement therapy. For most contraceptive applications, these rings are left in place for 21 days and then removed for 7 days to allow a menstrual cycle to take place.[84]. In vaginal rings, drug is homogeneously dispersed within a polymeric ring. In preliminary step, the drugs from outermost layer get release by burst mechanism. But it has been seen that the

con stint release of drug takes place from sandwich / reservoir type of vaginal ring. Recent advancement indicates that rings have been made on the original two-layer ring system by adding a third, rate controlling elastomer layer which contains no drug. A modern system in vaginal ring is a dual release contraceptive ring. This system con trains estrogen and progestin particles dispersed in aqueous polyether xylene glycol (PEG) throughout the silicone elastomer ring. This system delivers both drugs, at a constant rate, with approximately zero order kinetics.[85] The U.S. markets have introduced a vaginal ring (Nova Ring[er]) which is flexible, transparent and contains two active compo nets such as levonorgestrel and ethinyl estradiol. The vaginal ring releases 120 µg/day of levonorgestrel and 15 µg/day of ethinyl extra diol over a 3-week period[85].

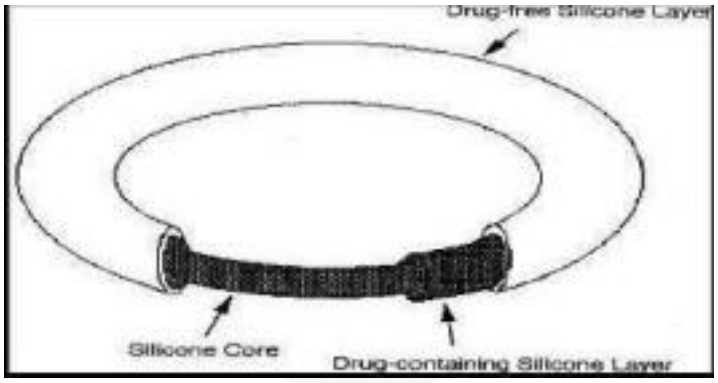


Figure 7: Vaginal Ring

Clinical acceptability of ring made up of ethylene vinyl acetate is very high because of its increase flexibility, improved optical properties, greater adhesion and increased impact and punch resistance[86].

7.4 Vaginal Films

The administration of potential microbicide drugs into the vagina is made possible by quick-dissolve film dosage forms. Films may be more user-acceptable than gels because they are less messy and easier to apply. Research to determine the optimal formulation conditions. It is also imperative that physiologically appropriate product assessment techniques be developed for vaginal film product development.

In trials of gels, women noticed certain concerns with product acceptability that can be resolved by polymeric films. Since the films are a reliable dry drug delivery technique, product leakage's "messy" discharge is avoided. Once in contact with the vaginal fluids, the

films quickly breakdown without introducing more fluids, decreasing leaking. Additionally, their rapid dissolving nature ensures quick release once inserted. Polymeric vaginal films offer an advance in vaginal formulation technology. Vaginal films may offer benefits such as simpler application, cheaper product cost, higher patient acceptability, longer medication stability, and increased patient acceptability. An acceptability study conducted by investigators at the University of Alabama [87] showed that Women preferred film formulations over other vaginal formulations like gels, foams, and suppositories. The small size of the film and the lack of the need for applicators results in a less expensive product that is easier to store. Reduced cost is an important consideration in developing nations as well as in the USA.

Advances in the field of polymer sciences have increased interest in the development of drug delivery systems which utilize newly available polymeric materials. Polymeric films are increasingly being used as a means of drug delivery [88-91]. A well-known example is the Listerine® pocket pack breath strip which provides similar oral antibacterial agents as found in the liquid formulation of Listerine®. Films for the oral delivery of vitamins, minerals, herbal remedies, supplements, cold remedies, pain medications, and gastric disturbance medications have been developed[90]. Polymeric films provide rapid drug release and bioadhesive properties that may increase retention time at the target tissue. Film-formulated products are very convenient for the user as well as easy to apply. Vaginal films have been investigated for use as contraceptives and more recently as microbicide formulations [92].

More recently, research has been conducted for the use of polymeric vaginal films as contraceptives and as micro biocide formulations [92]. There are several attributes which make vaginal films attractive as a microbicide product dosage form., few reports have been published using vaginal films as microbicides. A polystyrene sulfonate (PSS) microbicide film has been recently developed. PSS is a novel noncytotoxic antimicrobial contraceptive agent, which has been shown to be safe for vaginal administration in phase I clinical trials in a gel dosage form. The films were colorless, transparent, thin, soft, and tough and rapidly dissolve in physiologic fluid to form a smooth, viscous, and bioadhesive solution. Formulation of these films comprised a polymeric base with polyvinyl alcohol (PVA) combined with either hydroxyl ethyl cellulose or hydroxyl propyl methylcellulose and the addition of a plasticizer that varied among glycerin, poly ethylene glycol, and sorbitol [92].

Another study investigated the effects of cellulose acetate 1,2-benzenedicarboxylate (CAP), a film-coating ex accipient, to inhibit infection by cell-free and cell-associated. Most recently, an RC-101 vaginal film has been devil opted, and results were presented at the Microbicides 2008 annual meeting held in New Delhi, India. RC-101 is a synthetic analog of retrocyclin that has shown activity against X4 and R5 strains of HIV-1 in vitro, indicating potential as a microbicide. A PVA polymeric vaginal film formulation containing RC-101 (100 go/film) was developed by aqueous solvent recasting. RC-101 film product was clear, flexible, had smooth surfaces, and dissolved in less than 5 min in water. In vitro permeability studies in a Franz cell model using excised ectocervical tissue were also conducted. These studies compared permeability for tissue exposed to an RC-101 solution and tissue exposed to RC-101 formulated in a film dosage form. Both permeability evaluations resulted in no detectable amounts of RC-101 in the receptor chamber after 6 h as quantified by high-performance liquid chromatography analysis, suggesting no potential for systemic absorption. [6]

7.5 Vaginal Powder [8]

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. [42]

Figure 8: Vaginal Powder[44].

7.6 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. [42]

Figure 9: Vaginal Capsule[44]

7.7 Vaginal Ointments

There is an oil phase and an aqueous phase in vaginal ointment. Drugs like alendronate, clodronate, tiludronate, pamidronate, etidronate, ibandronate, etidronate, etidronate, zoledronate, or patronage that have been dissolved in aqueous phase and oil phase that has been added are the major ingredients in vaginal ointment[44].

93

Figure 10: vaginal ointment

7.8 Hydrogels:

The gelation and preservation of in situ-gelling vaginal formulations may constitute a turning point in the development of therapeutic medication efficacy. When mixed with aqueous solution, the phase-change polymers patronage and polyoxymethylene create thermally reversible gels. Phase shift polymers, such as poloxamer, exhibit the sol-gel transition in response to changes in body temperature, pH, and certain ions, and they extend the dosage form's duration in the vagina. In order to give a sustained release of active substances such nonoxynol, progestins, estrogens, peptides, and proteins in a vaginal environment, formulations based on a thermoplastic graft copolymer have been created. Within a short time

after application, non-aqueous solutions of the copolymer in hydrophilic excipients gel in place. These liquid compositions for in situ gelling[42].

Method of preparation of gel[11]:

- The cold method was used to prepare the vaginal inset gel.
- The prefer quantity of drug is weighed and dissolve in saline phosphate buffer in aseptic conditions.
- Preservatives was added at same time.
- Meanwhile the mixtures of polymers were kept aside for 24 hours for proper mixing.
- Next the drug and polymeric solution was mixed properly and the intended quantity was added to the isotonic solution.
- Solution was transferred into amber colored bottle and sealed till further use and resulting solutions were sterilized by autoclave at 121°C for 20 min at 15 PS.

8. Nanoparticles for Targeted Microbicide Delivery:

The targeted administration of microbicides into the vaginal tissue using nanoparticles is a recent approach that has been studied. To get around common drug problems like biological half-life, conformational stability, physicochemical stability, solubility, and immunogenic response, all of which may lead to decreased activity, nanoparticles made of poly (D, L-lactide-co glycoside (PLGA)) are currently being investigated for a variety of therapeutic applications. Nanoparticles can help vaginal microbicides penetrate the vaginal and ectocervical mucosa more easily, allowing the medicine to reach HIV target cells while still protecting the active ingredient. For PSC RANTES, a CCR5 chemokine receptor inhibitor, a biodegradable nanoparticle drug delivery method has recently been created[94].

9. VAGINAL IMMUNIZATION:

Numerous examples of successful vaccination using DNA vaccines given via various mucosal routes have been made in recent years. The vagina is regarded as the main site for pathogen introduction into the human body among the mucosal pathways. Systemic and mucosal immunity are both produced via mucosal immunization using DNA vaccines. Numerous vaginal vaccine formulations against a range of diseases, including the human

immunodeficiency virus, are now being researched (HIV). In a different investigation, mice infected intravaginally with the influenza A virus developed mucosal and systemic immunity to the HIV type-1 epitope [95].

Recent research has shown how to create and administer plasmid DNA vaccines to mucosal inductive tissues, such as the vagina. The female-generated track has the ability to trigger both cellular and humoral immune reactions to locally present antigens. It has been demonstrated that vaginal immunization of rats, people, and non-human primates causes serum and secretory IgA and IgG responses. The researchers administered suppositories containing plasmid code for the glycoprotein to cows intravaginally in an effort to immunize them against bovine herpes virus-1. A more recent strategy for the management of infectious diseases is represented by DNA vaccines [96].

10. Bioadhesive microparticles (microspheres or microcapsules):

There are a lot of vaginal microparticle delivery systems available nowadays. In the form of tablets for vaginal delivery, sustained release bioadhesive keto econazole microcapsules were created. By employing sodium carboxymethyl cellulose as a coating material and the phase separation process, ketoconazole microcapsules with core-wall ratios of 1:1 and 1:2 were created. A good sustained action was noted with microencapsulated tablets in dissolution trials of microcapsules, tableted microcapsules, and commercial ovules. Chitosan was suggested as a mucosal medication carrier for vaginal-uterine therapies. Chitosan was proposed as a drug carrier for mucosal administration in vaginal-uterine therapies based on its bioadhesive property and *in vivo* biodegradability under the action of hydrolases. A good example is the delivery of 5-aminosali cyclic acid to the colon. Microparticles may need to be cross-linked to retard their degradation in acidic media; but the cross-linking with glutaraldehyde introduces cytotoxic characteristics and depresses bio adhesion. Alternative cross-linking approaches are described along with the suitability of chitosan for the vaginal delivery of vac cine[97].

11. Vaginal noisome and liposomes

Recently, lipoidal particle drug delivery systems like lip some's and noisome were introduced which are playing an important role for delivery of proteins and peptides through vagina. In order to develop alternative formulations for the vaginal administration of clotrimazole which would provide sustained and controlled release of the appropriate drug for local vaginal

therapy, liposomes/noisome were evaluated as delivery vehicles. To optimize the preparation of the liposomes/noisome with regard to size and entrapment efficiency, multilamellar liposomes/ noisome containing the drug were prepared by a lipid hydration method. The liposomes/noisome thus prepared were evaluated for their stability as drug-loaded liposomes/noisome in simulated vaginal fluid at (37±1) °C. The two vesicle systems were also evaluated with reference to rat and rabbit vaginal irritation.[98]

12.Vaginal micro-emulsions

An interesting vaginal delivery system is in the form of an emulsion-based formulations designed to deliver antifungal agents such as imidazole. The system does not seep from the vagina and is designed to give controlled delivery for 3 or more hours. The use of microemulsions as drug delivery vehicle has been an exciting and attractive area of research because of its potential and extraordinary benefits. Microemulsions offer an interesting and potentially quite powerful alternative carrier system for drug delivery because of their high solubilization capacity, transparency, thermodynamic stability, ease of preparation, and high diffusion and absorption rates when compared to solvent system without surfactants. A recent study was conducted on intravaginal toxicity of a gel-microemulsion formula ton of spermicidal vanadocenes in rabbits which include *in vitro* and *in vivo* studies.[99]

Some of the experimented vaginal drug delivery system

Therapeutic drug	Intended use	Dosage form	Animal model	Comments
Nonoxynol-9	Spermicide/topical l contraceptive	l contraceptive	Rabbit	Detergent type spermicide, irritation and increased risk of infection
Miconazole nitrate	Anti-fungal	Cream, suppository, swelling controlled release system	In vitro	
Prostaglandin E2	Cervical ripening	Crosslinked PEG hydrogel, suppository	In vitro	Onset of labor not always predictable

Lactobacilli strains	Urogenital tract infections	Bi-layered tablet	In vitro	Restoration of normal vaginal flora, good bacterial viability in tablets
Progestin, levonorgestrel, norethindrone acetate	contraceptives	Vaginal ring	Human	Uterine bleeding, hormonal side effects, expulsions
estradiol	Hormone replacement therapy	Vaginal ring	Human	Risk of endometrial proliferation
Relaxing	Cervical ripening	Gel	Human	Decreased incidence of cesarean deliveries, reduced maternal-fetal morbidity
LHRH	Hormone dependent mammary tumors, fertility control	Suppository	Rat	Suppress secretion of ovarian steroids
Leuprolide	Ovulation inducing activity	Solution suppository,	Rat	Activity increased by 5 times with addition of absorption enhancers
Insulin	Diabetes mellitus	Solution, gel	Rabbit, rat	Low bioavailability

Commonly used marketed vaginal product

Therapeutic Drug (Brand Name)	Intended Use	Dosage Form	Comments	Company
Oxyquinoline sulphate, ricinolein 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.

Levonorgestrel, ethinyl estradiol (NuvaRing ®)	Contraceptive	Vaginal ring	Commonly reported adverse events are vaginitis, weight gain	Organon
Nonoxynol -9 (Conception®)	Contraceptive	Vaginal gel		Advance Care Product
Progesterone	Infertility, secondary	Vaginal gel	Possible side effects	Fleet Laboratories
(Prochoice®)	amenorrhea		are breast pain, constipation	
Clotrimazole (Triazole®)	Anti-fungal	Cream	Minor skin irritation	Taro Pharmaceuticals
Metronidazole (Metro gel Vaginal®)	Bacterial vaginosis	Vaginal gel	Vaginal discharge.	3M Pharmaceuticals
Progesterone (Corinne®)	Infertility, secondary amenorrhea	Vaginal gel	Bioadhesive sustained release in nature.	Serono
Estradiol (Vagile®)	Atrophic vaginitis	Vaginal tablet	Mild allergic reaction.	Novo Nordisk
Inopportune (Prost in E2®)	Labor inducer	Vaginal gel		Pharmacia
Tioconazole (Triazole®)	Anti-fungal, vaginal Candida infection	Vaginal ointment	Possible side effects are swelling of face, lips, tongue.	Bristol Myers Squibb
Estradiol (String®) Hormone therapy		Vaginal ring	Can increase the vaginal secretion	Pharmacia and Upjohn

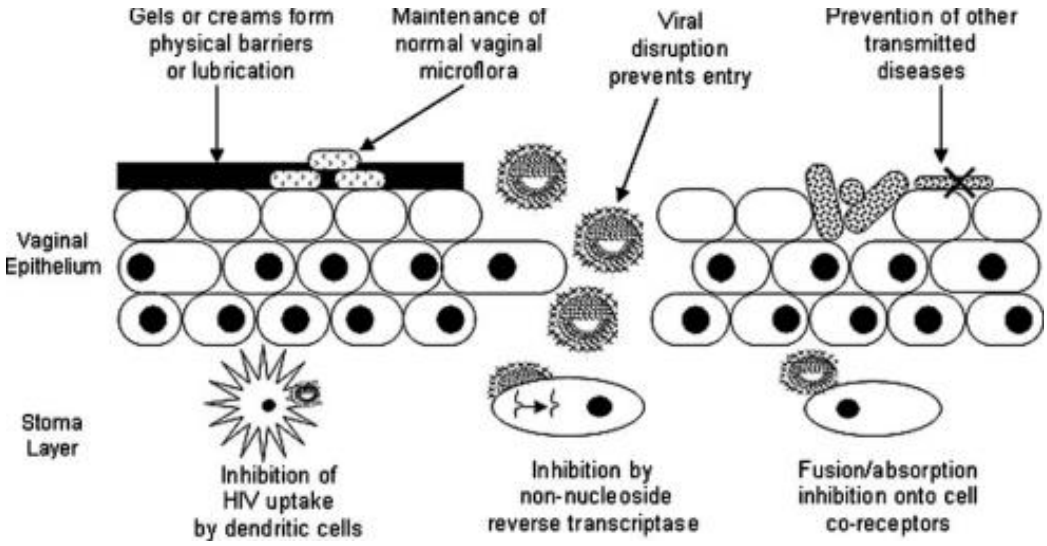
Inopportune (Cervidae®)	Induction of labor	Suppositories	Side effect like abdominal cramp, diarrhea may occur.	Controlled Therapeutics

Status of vaginal formulations in clinical trial stage

Formulation	**Phase**	**Purpose**	**Status**
Naphthalene 2-sulphonate (polymer) gel	Phase I	Determine whether the vaginal gel PRO 2000/5® causes irritation when used	Completed
PRO 2000/5® gel	Phase I	Determine the safety and acceptability when used by women;	In progress
Tenofovir PMPA gel	Phase I	Evaluate the PMPA gel in HIV-infected and HIV-uninfected women	In progress
Effectiveness of Buffer Gel® as a Vaginal Contraceptive	Phases II and III	Compare Buffer Gel® to Gyno II®, a currently available contraceptive gee	In progress
1.0% C31G SAVVY® vaginal gel	Phase III	Determine the effectiveness and safety for the prevention of male-to-female transmission of HIV among women	In progress
6% cellulose sulphate vaginal gel	Phase III	Determine the effectiveness and safety for the prevention of HIV infection	In progress
Nonoxynol-9 (N-9) gel	Phase III	Determine if it can prevent the spread of HIV	In progress

13. Novel concepts in vaginal drug delivery /Recent Advances in Vaginal Drug Delivery -Bioadhesive delivery systems

MICROBICIDE DRUG DELIVERY SYSTEMS: Current Intravaginal Microbicide Delivery Methods for Preventing the Transmission of STIs and HIV Conventional semi-solid aqueous gels and vaginal ring formulations make up the majority of the microbicidal delivery systems for intra vaginal administration that have been created and tested in ongoing clinical trials. A single dose of a microbicidal agent is intended to be delivered using these.[101-105]. A wide range of pharmacological dosage forms, including semi-solids, tablets, capsules, pessaries, liquid preparations, vaginal films, vaginal rings, foams, and tampons, have been created as intravaginal delivery systems for microbicides. Currently, the maximum duration of drug release for intravaginal microbicidal delivery systems is as follows: (1) Vaginal gels (6 h) [105,106], (2) vaginal tablets (8 h) [107,108] and (3) vaginal rings (71 days) [73].



Major developments in the field of microbicidal delivery over the past ten years have resulted in a variety of delivery systems in varying stages of development. [109]. The design of the delivery system, the microbicidal agent, and vaginal physiology must all be taken into account for an intravaginal microbicide delivery system to be ultimately successful. Additionally, a variety of physiological factors influence bioavailability, including the menstrual cycle, pH changes, and the presence of co-pathogens can all affect how well the formulation delivers the microbicide.[110,111]

However, only a small number of these formulations have been examined in Phase I/II clinical studies with HIV-infected and HIV-uninfected individuals.[112]. In order to develop

systems for quick clinical applications, many groups are now conducting or planning multi-center Phase I/II safety and Phase II/III efficacy studies in diverse geographical regions.

Design of Intravaginal Microbicide Delivery Systems

Intravaginal delivery may be designed for administration of microbicides by using an applicator or specifically designed systems for intravaginal administration. In general, based on the delivery system or the microbicide used, drug absorption, distribution and residence time in the vagina may vary. Early studies by Johnson and Masters[113] demonstrated how the type of delivery system has a significant impact on the distribution of the microbicide in the vaginal tissue. Tablet dosage forms were outperformed more by solutions, suspensions, and foams. A vaginal delivery system should ideally distribute uniformly throughout the vaginal cavity and be designed for localized microbicidal distribution. This means that fast dissolving solid systems or semi-solid systems are necessary for a local effect to occur in the vagina. Topical effects are better served by intravaginal rings or bioadhesive delivery devices. The bioavailability of the majority of intra vaginal microbicide delivery devices with prolonged vaginal exposure is currently unknown.[112,114]

Creams and Gels:

Till date, creams or gels make up the vast majority of intravaginal medication delivery solutions for microbicides. These systems are messy, uncomfortable, and may not deliver an accurate dose due to non-uniform distribution and leaking, despite being often employed for the topical intravaginal delivery of microbicides. [115]. Lamont et al. tested the effectiveness of a 3-day regimen of clindamycin vaginal cream in treating bacterial vaginosis.[116] carried out a randomized, placebo-controlled study on pregnant women and discovered for instance, the effectiveness of a 3% alginate gel containing nonoxynol-9 as an intravaginal spermicidal agent[117]. The research discovered that the formulation's pH and osmolarity had an impact on the agent's spermicidal action as well as its diffusion. Recently, a gel microemulsion-based spermicide formulation with an anti-HIV activity was created using the zidovudine phenyl phosphate derivative.[118]. Multiple intra vaginal applications of this drug as a microemulsion gel formulation did not cause any damage in the vaginal epithelium in the rabbit model[16].

Tablets and Suppositories

A large number of intravaginal delivery systems are also available in the form of tablets or suppositories. Other vaginal tablet-like forum lotions are extrapolations of silicone-based vaginal rings. Research groups have studied the release of microbicides from silicone matrices[132,120].

Vaginal Rings

Vaginal rings are circular ring-type drug delivery devices designed to release microbicides in a controlled manner after insertion[32]. In simple vaginal rings, the microbicide is homogeneously dispersed within a polymeric ring with the surface of the ring releasing the microbicide faster than the inner layers. The key challenge in development of these systems is finding the optimum dose that will deliver the least amount of microbicide necessary to ensure protection[120]. Advances have been made on the original two-layer ring system by adding a third, outer, rate controlling drug-free elastomer layer to minimize the drug concentration spike[21].

Most women judged the ring easy to insert and remove, and no side-effects were experienced [121,78].

Bioadhesive Intravaginal Systems:

Bioadhesive polymers that have been used for intravaginal formulations include polycarbophil, hydroxypropyl hydroxy propyl and polyacrylic acid[123].The first bioadhesive systems for vaginal drug delivery were in the form of tablets for the delivery of bleomycin, an anti-cancer agent [123,38,9,30,124].

ADVANTAGES:

- This is a better delivery system in case of nausea and vomiting[125].
- Stomach and intestinal irritation can be avoided[125].
- Hepatic first pass elimination can be avoided[42].
- As there is no contact with digestive fluid, enzymatic degradation of drugs is avoided[125].
- Drug delivery can be stopped by removing the dosage form e.g., Vaginal rings[125].

- Rapid drug absorption and quick onset of action is achieved[125].
- When compared to parenteral medication in terms of patients on long term therapy, this system is convenient[125].
- Self-medication is possible[58].
- It permits continuous and prolonged residence of the dosage form at the site of application[58].
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by another parenteral route [58].
- The self-insertion and removal of the dosage form is possible[58].
- Drugs, which traditionally are only given parental, may be administered vaginally either as such or in combination with absorption-promoting additives[126].
- Convenient for the patients, especially for those on long-term therapy, when compared with parenteral medication[188].
- The vaginal bioavailability of smaller drug molecules is good[126].
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach[126].

LIMITATIONS:

- Influence of the estrogen concentration on the permeability of the vaginal membrane, which can influence the pharmacokinetics of drugs designed for systemic action [127,128].
- The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) [129] and this amount is decreasing with increasing age. This volume may also affect the vaginal absorption of drugs.
- The pH of the vaginal fluid is also a factor which affects the drug absorption as the unionized forms will be preferably absorbed[130].
- Some of the drugs are sensitive at the vaginal pH[130].
- Gender specificity[130].
- Sometimes leakage of drugs from vagina and wetting of undergarments [78].

- Local irritation of some drugs[130]
- Influence of sexual intercourses[130]
- Personal hygiene[130]

APPLICATION OF VAGINAL DRUG DELIVERY SYSTEM:

This route of drug administration is useful for vaginal immunization.

• Multi-cycle administration of vaginal contraceptive rings.

• Effective route for the treatment of HIV infection.

• Effective route for the treatment of local fungal infection.

• Effective for the delivery of hormones.

CONCLUSION:

The vagina still remains to be an unexplored route of drug delivery. Although the human vagina is used as a route for local action in the cervical-vaginal region, its adoption for systemic delivery of macromolecules still needs to be accomplished. Various therapeutically important drugs such as insulin, calcitonin and sex hormones have been attempted to deliver via vaginal route but there is not much success in the development of safe and viable vaginal formulations for these macromolecular drugs. Among the drug delivery systems available for this route, intravaginal gels for labor induction have been found to be potential vaginal drug delivery systems mainly because of their bearing on childbirths. Bioadhesive vaginal formulations are likely to emerge as new vaginal formulations for both local and systemic delivery. With the increasing number of novel polymers each year, challenge remains to design appropriate bioadhesive vaginal formulations. Vaginal rings have shown significant promise and are well accepted within the female population. Several combination vaginal contraceptive rings have been found to provide excellent contraceptive efficacy with little risk of adverse effects. More sophisticated and programmable vaginal rings could be developed in the near future for systemic delivery of therapeutically important macromolecules.

Another area that needs to be investigated in detail is the application of immunization via the vagina.

With the pandemic increase in the number of HIV infected individuals every year worldwide, the development of an effective vaginal vaccine rendering local immunity becomes imperative. One of the real challenges for future vaginal drug delivery will be to recognize ways to subjugate the complex biological barriers that limit the delivery of small and macromolecular drugs.

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