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Review Article

A REVIEW ON VAGINAL ROUTE AS A SYSTEMIC DRUG DELIVERY

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ABSTRACT

Exhaustive efforts have been made to the administration of drugs, via alternative routes, that are poorly absorbed after the oral administration. The vaginal route of drug delivery has been known since ancient times. In recent years, the vaginal route has been rediscovered as a potential route for systemic delivery of peptides and other therapeutically important macromolecules. However, successful delivery of drugs through the vagina remains a challenge, primarily due to the poor absorption across the vaginal epithelium. The rate and extent of drug absorption after intra vaginal administration may vary depending on formulation factors, vaginal physiology, age of the patient and menstrual cycle. Suppositories, creams, gels, tablets and vaginal rings are commonly used vaginal drug delivery systems. The purpose of this communication is to provide the reader with a summary of advances made in the field of vaginal drug delivery. This report, therefore, summarizes various vaginal drug delivery systems and factors affecting drug absorption from the vaginal route. The objective of this paper is to provide an overview of various vaginal drug delivery systems currently in development stages are available in the market, immunization via the vagina and special emphasis on the challenges and difficulties associated with systemic delivery of drugs via the vaginal route.

KEYWORDS vaginal tablet, vaginal rings, bio adhesive system

1. Introduction:[1],[2],[3]

Currently, there is a huge interest in the scientific community and drug industry to exploit various mucosal routes of delivering drugs, which are poorly absorbed after oral administration. Based on the numbers of scientific papers published in pharmaceutical journals over the last decade, it is apparent that the human vagina remains to be a relatively unexplored route of drug delivery despite its potential as a non-invasive route of drug administration. [1]The presence of dense network of blood vessels has made the vagina an excellent route of drug delivery for both systemic and local effects. The main advantages of vaginal drug delivery over conventional drug delivery are the ability to by-pass first pass metabolism, ease of administration and high permeability for low molecular weight drugs. However, several drawbacks, including cultural sensitivity, personal hygiene, gender specificity, local irritation and influence of sexual intercourse, need to be addressed during the design of a vaginal formulation. Further, considerable variability in the rate and extent of absorption of vaginally administered drugs is observed by

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changes in the thickness of the vaginal epithelium.

2. Anatomy and physiology of the vagina[3],[4],[5]

In the pharmaceutical literature, human vagina is often described as slightly S-shaped fibro muscular collapsible tubes between 6 and 10 cm long extending from the cervix of the uterus. The vaginal wall consists of three layers: the epithelial layer, the muscular coat and the tunica adventia. During the menstrual cycle, the thickness of the vaginal epithelial cell layer changes by approximately 200–300 Am. The surface of the vagina is composed of numerous folds, which are often called rugae. The rugae provide dispensability, support and an increased surface area of the vaginal wall. 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. The network of blood vessels that supply blood to the vagina include a plexus of arteries extending from the internal iliac artery, uterine, middle rectal and internal prudential arteries. In fact, arteries, blood vessels and lymphatic vessels are abundant in the walls of the vagina. Drugs absorbed from the vagina does not undergo first-pass metabolism because blood leaving the vagina enters the peripheral circulation via a rich venous plexus, which empties primarily into the internal iliac veins. There is some drainage to the haemorrhoidal veins as well. The lower part of the vagina receives its nerve supply from the prudential nerve and from the inferior hypogastria and uterovaginal plexuses.

Although the vagina does not possess any gland, it secretes a large amount of fluid. Cervical secretion and transudation from the blood vessels with desquamated vaginal cells and leucocytes mainly constitute the vaginal fluid. Secretions from the endometrium and fallopian tubes also contribute to the vaginal fluid. Like the thickness of the vaginal epithelium, the amount and composition of the vaginal fluid also change throughout the menstrual cycle. Women of reproductive age produce fluid at a rate of 3–4 g/4 h, while the discharge produced by postmenopausal women is reduced by 50% compared to that produced fluid may contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl ketones and aromatic compounds. Sexual arousal may affect the volume and composition of vaginal fluids and that can alter the drug release pattern from the vaginal delivery system. Lactic acid produced from glycogen by the Lactobacillus acidophilus present in the vagina acts as a buffer to maintain the vaginal pH between 3.8 and 4.2. During menstruation, the pH of vaginal fluid increases and frequent acts of coitus may also cause an increase in the vaginal pH because both ejaculate and vaginal transudate are alkaline. The presence of cervical mucus and the amount of vaginal transudate may also alter vaginal ph. The vaginal epithelium has a high activity of enzymes that could potentially affect short- and long-term stability of intravaginal delivery systems and devices.

3. Factors affecting the vaginal absorption of drugs[14],[22]

Like other mucosal routes of administration, drugs administered via the vaginal route are absorbed (i) transcellularly via concentration dependent diffusion through the cells, (ii) paracellularly mediated by tight junctions and (iii) vesicular or receptor

ISSN 2319-1082

mediated transport as pointed out by Richardson and Ilium.

Absorption of drugs from vaginal delivery systems occurs in two main steps: drug dissolution in vaginal lumen and membrane penetration. Any biological or formulation factor that affects the drug dissolution and membrane transport could potentially affect the absorption profile from vaginal drug delivery systems. Overall, vast and multifarious factors and processes are involved in drug absorption from the vaginal route.

3.1 Physiological factors[14]

As mentioned above, cyclic changes in thickness of the vaginal epithelium, fluid volume and composition, pH and sexual arousal could potentially affect drug release from intravaginal delivery systems. For example, the vaginal absorption of steroids is affected by the thickness of the vaginal epithelium. 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. Vaginal absorption of estrogen hasBeen shown to be higher in postmenopausal women compared to premenopausal women. There have Been some conflicting reports as to the change in drug absorption with the increase in vaginal epithelium. Studies have shown that the vaginal absorption of steroids is influenced by the thickness of the vaginal epithelium and the epithelial thickness is therefore reduced by long-term estrogen therapy. However, the vaginal progesterone absorption in estrogen deficient women who were receiving vaginal estrogen therapy was found to be increased , although prior estradiol therapy should have caused an increase in the vaginal epithelium thickness. This anomalous finding was explained by the fact that the absorption of progesterone was increased with increased vascularity of the vagina. Further cervical mucus of the vagina, which is a glycoprotein gel, could possibly be exploited for bio adhesive drug delivery. However, the presence of cervical mucus could also serve as a permeability barrier to prospective drug candidates. The volume, viscosity and pH of vaginal fluid may have either negative or positive impact on vaginal drug absorption. The absorption of a drug that is poorly water-soluble may be increased when the fluid volume is higher. However, the presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from vaginal cavity and subsequently reduce absorption. Since many drugs are weak electrolytes, the pH may change their degree of ionization and affect the absorption of the drug. In vitro study has shown that the release of PGE2 from vaginal preparations may vary depending on the pH of the media. Any change in the vaginal pH may affect the release profiles of pH sensitive drugs from vaginal drug delivery systems.

3.2. Physicochemical properties of drugs[23]

Physicochemical properties such as molecular weight, lipophilicity, ionization, surface charge, chemical nature can influence vaginal drug absorption. For example, the vaginal permeability of straight chain aliphatic alcohols increases in a chain length dependent manner. Similarly, vaginal permeability is much greater to lipophilic steroid such as progesterone and estrone than to hydrophilic steroid such as hydrocortisone and testosterone. However, it is generally accepted that low molecular weight lipophilic drugs

ISSN 2319-1082

are likely to be absorbed more than large molecular weight lipophilic or hydrophilic drugs. A study on vaginal absorption of polyvinyl alcohol suggested that the molecular weight cut-off above which compounds are not absorbed may be higher for the vagina than other mucosal surfaces. Since vaginal fluid contains a large amount of water, any drug intended for vaginal delivery require a certain. Degree of solubility in water. In fact, data on the human vaginal permeability of drugs with different physicochemical properties is very limited; much work needs to be done on the effects of physicochemical parameters of drug on vaginal absorption.

3.3.Vaginal absorption of drugs:[20]

Drugs are transported across the vaginal membrane by the transcellular route, intracellular route or vesicular and receptor mediated transport mechanisms. A physical model of the vaginal membrane as a transport barrier has been described. The physiological factors (e.g. cyclic changes in the thickness and porosity of the epithelium, volume, viscosity and pH of the vaginal fluid) and physicochemical properties of drugs (e.g. molecular weight, lipophilicity and ionization) affect absorption across the vaginal epithelium. The absorption of drugs, targeted for local action in the vagina, is not desirable.

4. Vaginal enzymes in different species[28]

The external cell layers and the basal cell layers of the vagina retain most of the enzyme activity Among the enzymes present, proteases are likely to be the prominent barrier for the absorption of intact peptide and protein drugs into the systemic circulation. It has also been reported that the rat vaginal smears have trypsin-like activity, which reaches a maximum level during the estrus stage. Lee has suggested that most of the exopeptidases and endopeptidases, which digest the peptides and proteins are present in the vaginal epithelium. The various enkephalins studied in rabbit vaginal epithelium suggest the presence of at least three peptidases viz. aminopeptidase, dipeptidyl peptidase and dipeptidyl carboxypeptidase, which play a vital role in metabolism of enkephalins. Among these enzymes, aminopeptidases were the main enzymes responsible for methionine and leucine enkephalin metabolism, while dipeptidyl carboxypeptidase was the main enzyme for d- Ala-met-enkephalin metabolism. Sayani et al. Reported the existence of aminopeptidases in rabbit nasal, rectal and vaginal extracts. The highest concentration of these enzymes was in the vaginal extract (0.045 U/ml) of the rabbit. A specific study dealing with the comparison of an enzymatic activity of four different aminopeptidases (aminopeptidase N, leucine aminopeptidase , aminopeptidase A and aminopeptidase B) in vaginal homogenates of various species report that the enzyme activity in rat, rabbit and human was significantly lower than that of sheep and guinea pig. Overall, the aminopeptidase activity in the species showed the following order of activity: Sheep,guinea-pig,rabbit,human,rat. 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 vagina.

5. Drug delivery systems for vaginal administration[36],[67]

ISSN 2319-1082

Traditionally, solutions, suppositories, gels, foams and tablets have been used as vaginal formulations. More recently, vaginal ring has been introduced for hormone replacement and contraceptive therapy. In general, based on the drug delivery system or formulations used, drug absorption, distribution and residence time in the vagina may vary. In fact, early work in this field the drug distribution and coverage of vaginal tissue varies considerably with the nature of the delivery system; solution, suspension and foam showing greater superiority over tablet dosage form. Ideally, a vaginal drug delivery system that is intended for local effect should distribute uniformly throughout the vaginal cavity. Ideally, the choice of vaginal drug administration depends on the applicability of the intended effect; whether a local or topical effect is required,For a local effect to occur, semi-solid or fast dissolving solid system will be required. For a topical effect, generally, a bioadhesive dosage form or intravaginal ring system would be more preferable. However, by far, it had been difficult to quantitatively measure the distribution of a drug after an intravaginal administration and also it is uncertain if the administered formulation coated the whole organ. In this regard, an interesting helpful. Vaginal delivery may be designed for the administration of drugs by using an applicator or specifically designed systems for intravaginal administration. Further, vaginal formulations may be designed to Produce local effect such as spermicidal or antibacterial effects or to produce a systemic effect by continuous release of drugs such as contraceptives. Few of the commonly used marketed preparations With their intended states are tabulated in Table 1.

5.1. Creams and gels[65]

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 developingtopical 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

ISSN 2319-1082

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 off 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 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, phenyl 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 mucosal 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, Shetty et al. 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 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 Danielian et al. 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 significant differences in the requirement of analgesia, mode or delivery, or neonatal outcome were noticed between the two cohorts.

ISSN 2319-1082

TABLE 1: List of vaginal preparations recently developed or under development

Preparation	Active ingredient	Company	Status
Acidform (gel)	–	TOPCAD (IL, USA)	Phase I/II clinical trials
Advantage-S (gel)	Nonoxynol-9	Columbia Laboratories (FL, USA)	Market
BufferGel™ (gel)	–	ReProtect (MD, USA)	Phase I clinical trials
ccvr	–	Organon (NJ, USA)	Phase III clinical trials
Cleocin (cream)	Clindamycin phosphate	Pharmacia & Upjohn (MI, USA)	Approved (USA)
Crinone® (gel)	Progesterone	Wyeth–Ayerst Laboratories (PA, USA)	Approved (1997)
Efamast	Evening primrose oil	Scotia Holdings (Surrey, UK)	Phase II clinical trials (Europe)
Estradiol	17-b-estradiol	Watson Pharmaceuticals (CA, USA)	Phase II/III trials (USA)
Estring Vaginal Ring	Estrogen	Pharmacia & Upjohn (MI, USA)	Approved (1998)
Femstat one (Emulsion)	Butoconazole	Hoffmann–LaRoche Laboratories (NJ, USA)	Approved (USA)
Gynol II jelly	Nonoxynol-9	Ortho Pharmaceuticals (NJ, USA)	Market
Invisible condom	Thermoreversible gel	Laval University (Canada)	Phase I clinical trials
LASR Suppository	Nonoxynol-9	Advanced Care Products (NJ, USA)	Phase II clinical trials
Pro 2000 (gel)	Napthalene 2-sulfonate	Procept (MA, USA)	Phase II NIAID trial
Replens® (gel)	–	Columbia Laboratories (FL, USA)	Market
Savvy™ (gel)	Glyminox	Biosyn (PA, USA)	Phase I clinical trials

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, bothmisoprostol 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

ISSN 2319-1082

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 Shetty et al. 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 out 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 (25mg) is efficacious and safer than the 100 mg oral doses. Different methods of misoprostol administration may not be equivalent with regard to efficacy and safety.

5.2. Suppositories and vaginal tablets[62]

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 candiasis and progesterone for hormonal replacement therapy. 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

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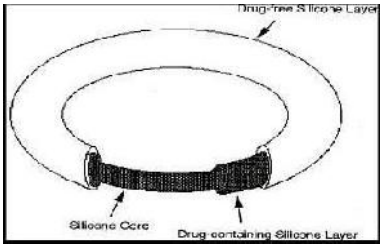
drugs may not be suitable for vaginal tablets. Presence of penetration enhancers such as surfactants, bile salts can significantly enhance absorption.

5.3. Vaginal rings[57] ,[58],[59][60]:

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 ring are that it is user controlled, does not Interfere with caution, does not require a daily intake of pills and allows continuous delivery of low dose Steroids. They are approximately 5.5 cm diameter with a circular cross section diameter of 4–9 mm and The ring are inserted in the vagina. In simple vaginal rings, drug is homogeneously dispersed within a Polymeric ring. 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 A 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 non-medicated central core and a nonmedicated 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. The rate of drug release can be modified by changing the core diameter or thickness of the nonmedicated 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 bartender 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. Further, the clinical acceptability of rings made of ethylene vinyl acetate is very high. In a study by Roumen and Dieben, evaluating the tolerability of ethylene vinyl acetate nonmedicated vaginal ring of diameter 54 mm, the acceptability present 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. NuvaRingR is the only combined contraceptive vaginal ring available in the US market.



Vaginal Ring

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NuvaRing 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 NuvaRingR 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. EstringR is made of silicone polymers and when inserted in the vagina releases 7.5 mg of estradiol per day.Bioadhesive 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 vinyl acetate and styrene Butandiene 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:

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6.Novel concepts in vaginal drug delivery

Several aesthetic and functional qualities must be incorporated into VDFs. NVDDS need to be designed with desirable distribution,bioadhesion, retention and release characteristics. The conventional VDFs, such as suppositories, gels, creams and foams can meet some but not all of these requirements. These features can be achieved by the use of Bioadhesive and other novel delivery systems.

6.1. Bioadhesive 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–

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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 carbopol 934P polymer. The carbopol 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 antimycotic agent, clotrimazole, was developed by incorporating bioadhesive polymers viz. polycarbophyl, hydroxypropylmethylcellulose and hyaluronic sodium salt into suppositories made of semi-synthetic solid triglycerides. The authors argue that 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 to simulate vaginal conditions for 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.

6.2.Other novel delivery systems:

Phase change polymers such as poloxamers exhibit sol–gel transition in response to body temperature, pH and specific ions, and they prolong the residence time of the dosage form in the vagina. However, these can interfere with sexual intercourse.Formulations based on a thermoplastic graft copolymer have

been developed to provide the prolonged release of active ingredientssuch as nonoxynol, progestins, estrogens, peptides and proteins in a vaginal environment. Non-aqueous solutions of the copolymer in hydrophilic excipients

ISSN 2319-1082

undergo in situ gelation in a short period of time after application.These in situ gelling liquid formulations can provide the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and retention owing to the formation of a mucoadhesive gel. Although studied to a limited extent, liposomes also have the potential to provide the controlled release of a drug after vaginal administration.

7. Vaginal immunization[69],[70],[71][72]

In recent years, there have been several reports of successful immunization with DNA vaccines administered via various mucosal routes. Mucosal sites, including the vaginal route, represent the primary site of entry of pathogens into the human body. Most of the conventional vaccines are administered via the oral or parenteral route resulting in systemic rather than mucosal immunity. On the other hand, mucosal immunization causes mucosal as well as systemic immunity. In this regard, several Vaginal vaccine formulations are being continuously researched against a variety of pathogens, including the human immunodeficiency virus (HIV). A recent study reports the development of a novel HIV-CCR5 receptor vaccine for the control of mucosal simian (SIV) and human forms of the virus. The vaccine, which targets both the virus and its CCR5 receptor, was administered in female rhesus monkeys either by the vaginal route or by targeting the proximity of the draining iliac lymph nodes. This immunization strategy through the vagina was found to significantly inhibit SIV/HIV infection in the animal model and shows promise for a novel approach in the prevention of HIV transmission. In another study, intravaginal infection of mice with influenza A virus resulted in mucosal and systemic immunity against HIV type 1 epitope. DNA vaccines represent a new approach to the control of infectious diseases. An application of plasmid DNA vaccine to mucosal inductive tissues, including the vagina. The female genital tract has the capacity to produce humoral and cellular immune responses against locally encountered antigens. Vaginal immunization of rodents, human and non-human primates have been shown to elicit serum and secretory IgA and IgG responses in cervico-vaginal washes. Further, this route of immunization was ineffective in eliciting immune responses in other mucosal compartments. Rather than the simple application of vaccine formulation at the target site, an example of vaccine administration via vagina specific dosage form could best be illustrated by a seminal paper on mucosal immunity by Loehr et al. In an attempt to induce immunity against the bovine herpes virus-1 in cattle, the researcher's immunized cows intravaginally with suppositories containing plasmid coding for the glycoprotein D. The level of immunity obtained, as assessed by the level of IgG in serum and IgA in both serum and nasal fluids, was of sufficient magnitude to minimize weight loss and significantly reduce the duration of virus shedding. Such successful noninvasive DNA immunization in large animals could open avenues for a new area of mucosal immunization in humans.

8. Advantages of vaginal drug delivery system:[68],[84]

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

ISSN 2319-1082

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.
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.

9. Limitations of Vaginal Drug Delivery Systems:[63],[65]

Some of the drugs are sensitive at the vaginal pH.
Local irritation of some drugs.
Influence of sexual intercourses.
Gender specificity.
Personal hygiene.
Sometimes leakage of drugs from vagina and wetting of under garments.

10. 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 remains to be an underutilized route of drug delivery. Although the human vagina is used as a route for local action in the cervico-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 attempting to deliver via the vaginal route but there is not much success in the development of safe and viable vaginal formulations for these macromolecule 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, the challenge remains to design appropriate bioadhesive vaginal formulations. Vaginal rings have shown significant promise and are well accepted within female population. Several combination vaginal contraceptive rings have been found to provide excellent contraceptive efficacy

ISSN 2319-1082

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 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 macromolecule drugs.

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