

A Review on Novelty and Potentiality of Vaginal Drug Delivery

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Abstract: The objective of this review is to describe the potentiality of vaginal route and the current status of several intravaginal delivery systems. A number of exhaustive efforts have been made toward the administration of drugs, via alternative routes, that are poorly absorbed after the oral administration. The vagina as a 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. A great deal of interest has been noticed in the design and application of different dosage forms via the vaginal route. Several studies have proven that the vagina is an effective route for drug administration intended mainly for local action, but systemic effects of some drugs also can be attained. The major advantages of this route include accessibility, good blood supply, the ability to bypass first-pass liver metabolism, and permeability to large molecular weight drugs, such as peptides and proteins. This review, therefore, summarizes various vaginal drug delivery systems with an introduction to vaginal physiology and factors affecting drug absorption from the vaginal route.

Keywords : Vagina, Intravaginal delivery, HIV, Vaginal formulations.

Introduction

The present status of research and drug development is mainly focused on invention of new drug delivery systems and exploits different possible routes of drug delivery which will provide a huge degree of safety and optimum efficacy. Literature shows that over a last few decades vagina remain to be a relatively unexplored route of drug administration, though as a site of drug delivery it offers certain unique features that can be exploited in order to achieve desirable therapeutic effect. Traditionally from the past few decades vaginal routes is used mainly for the local pharmacological effect, eg: antimicrobial, spermicidal etc. Until 1920s vagina was considered to be an organ incapable of absorbing drugs systematically,^{1, 2} but the mucous permeability and dense network of blood vessels has made vagina an excellent route of drug delivery for both local and

systemic effect^{3, 4}. Some of the typical delivery systems administered via vaginal route include solution (foam, douches), aerosols, semisolids, (creams, ointments, gels), tampons, tablets, capsules, pessaries, suppositories, particulate systems, intravaginal rings, sponges and powders⁵.

The research work till done on this route of drug delivery system shows that, the permeation mechanism for most of the active substances are follows mainly diffusion. Whereas majority hydrophobic substances are mainly absorbed through intracellular route, while hydrophilic one are preferably absorbed by pores present in the vaginal mucosa⁶. In addition to that permeability of the vagina is strongly influenced by the estrogen concentration, which influence the pharmacokinetics of drug designed for systemic action⁷.

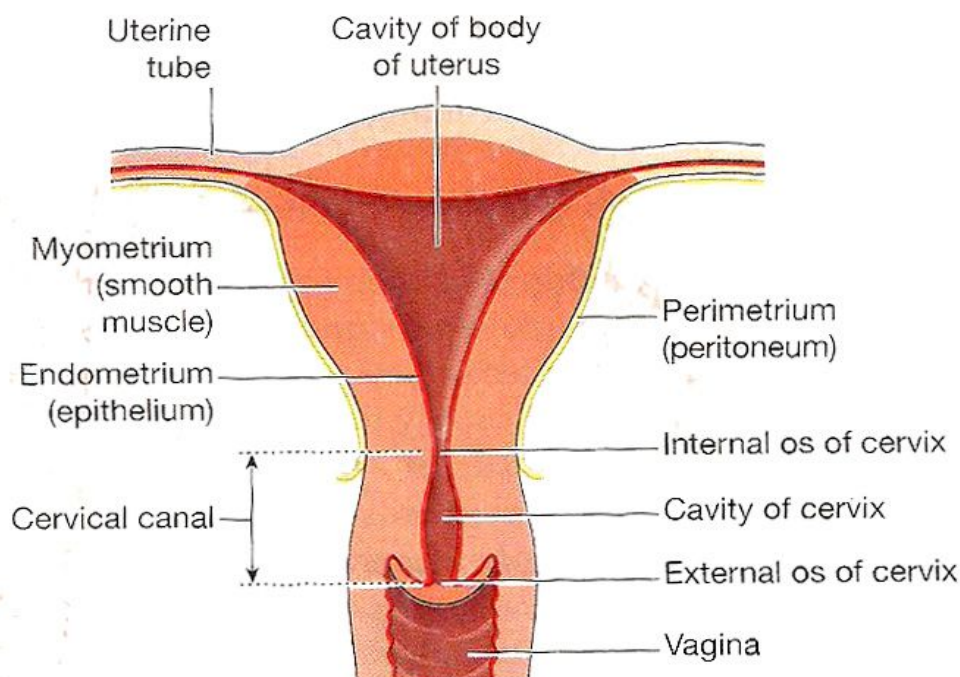


FIG-1 UTERUS AND UTERINE TUBE

The main advantages of vaginal drug delivery are mainly, avoidance fast pass metabolism, gastrointestinal irritation and side effect at gastrointestinal tract. It is easy to administrated and also provide a scope of self administration⁸. It has been found that Low molecular weight drugs shows higher permeability through this delivery system. However drug delivery through this route having several draw backs like low bioavailability, gender specificity, culture sensitivity, personal hygiene, local irritation, influence of sexual inter course and most importantly changes of physiological condition depending upon age need to be considered during the design of vaginal formulation⁹.

The present scenario shows that despite of several drawbacks, potentially important features of drug delivery via vaginal route gaining a growing interest in the field of research and development. Currently most of the works of vaginal delivery systems are mainly related to sexually transmitted diseases and prevention of HIV infections.

Vaginal Anatomy, Histology and Physiology

The vagina is a female genital organ, plays an important role in reproduction. Based on the literature we can describe vagina as a slightly S-shape fibro muscular, tubular organ, that approximately 6-10 cm long and extended from the cervix of the uterus to the vestibule^{10, 11}. As per radiographic colpographic study

vagina is a slightly curved organ with two distinct positions; a lower convex portion and a wider upper portion that lies in an almost horizontal plane at standing position of subject^{12, 13}. The angle between upper and lower axes is about 130 degree. When vagina enters to the pelvis region it passes through two diaphragms; the urogenital diaphragms and the pubococcygeus from the pelvic diaphragms, act as sphincters to the vaginal introitus. The women of reproductive age having numerous folds in vagina, named "rugae", which provide distensibility, support as well as increase surface area of vaginal wall¹⁴. 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. Due to this only women rarely feel localized sensation or any discomfort when they uses vaginal products like suppositories, tampons, vaginal ring etc., and often unaware of the presence of such items in the vagina¹. The vascular supply of vagina constructed of extended arteries that cover the vagina from multiple sources. One of the major features of vascularity of vaginal tissue that as attracted attention recently is the postulation of a fast uterine pass effect, or direct preferential vagina to uterus transport. A significantly higher concentration of progesterone in uterus after vaginal administration as compare to oral

administration can be taken as an evidence for the above findings¹⁵.

The vaginal histology is mainly consisting of four distinct layers. An estimated cell turnover of vagina is about 10-15 layer in order of 7 days. The superficial layer is mainly composed of nonsecretory stratified squamous epithelium; its 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 areolar connective tissue and a large plexus of blood vessels^{16, 17}. Vaginal tissue does not contain fat cells, glands or hair follicles¹⁸.

The vaginal physiology is mainly influence by age, hormonal balance, pregnancy, pH changes and concentration of microflora. Literature shows that major changes will be take place in vaginal physiology with age, like thickness of epithelium layer, concentration of several enzymes, and production of vaginal fluid and extent of vaginal discharge¹⁹. Human vaginal fluid mostly transudes from vaginal and cervical cells²⁰, which mainly contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl-ketones and aromatic compounds²¹. The composition of fluids is effected by cyclic changes caused by hormonal influence and state

of arousal, which can alter the drug release pattern from vaginal drug delivery system²². The thickness of vaginal epithelium, amount and composition of vaginal fluid also changes throughout the menstrual cycle. 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 transudate¹⁰. The lactic acid produced from glycogen by lactobacillus present in vagina plays an important role in maintains acidic pH environment.

Factors Affecting Vaginal Absorption of Drugs

The drug transport across vaginal membrane mainly takes place by three major ways, firstly transcellularly via concentration dependent diffusion through the cells, next is paracellularly mediated via tight junctions and last one is vesicular or receptor mediated transport. Drug absorption from vaginal delivery system is mainly takes place in two main steps: drug dissolution in vaginal lumen and membrane penetration, so any factors related to physiology or formulation that affects the above mentioned steps will potentially alter absorption profile from vaginal drug delivery. Some of the factors which influence the drug absorption are discuss in the following portion.

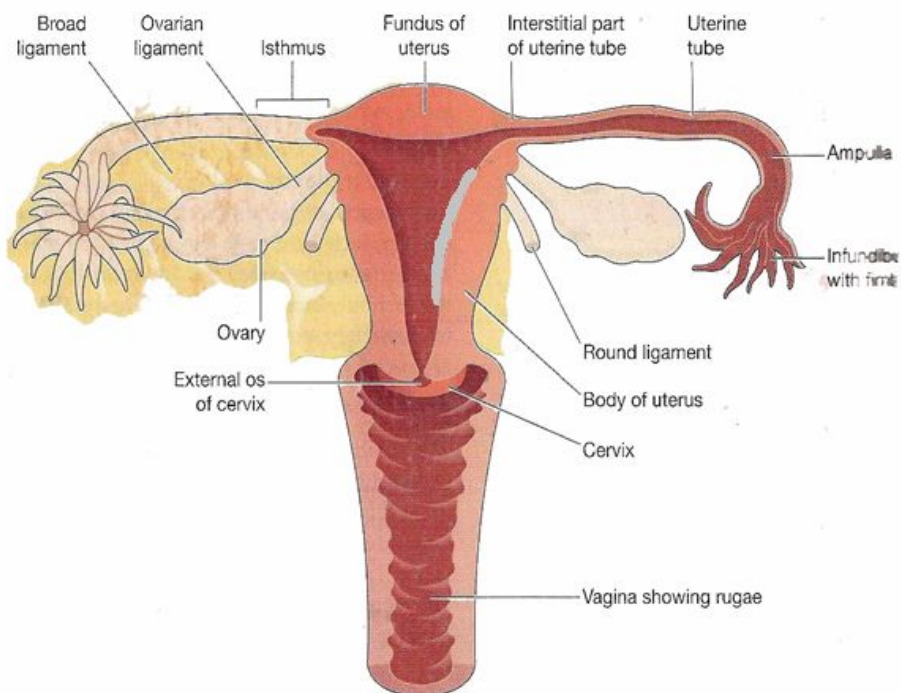


FIG-2. Different Major Segmental Portion of Female Reproductive Organ.

Physiological Factors

Physiological factors like changes in the thickness of epithelium layer, cyclic changes, changes in the status of enzyme, hormones, volume of vaginal fluid, alteration of vaginal pH and sexual arousal, as describe earlier can potentially affect drug release from any intravaginal delivery system and also alter its rate of absorption. For e.g. vaginal absorption of steroids is affected by the thickness of vaginal epithelium²³. Literature shows that vaginal absorption of estrogen shows high in post menopausal women compare to premenopausal women²⁴. The high volume of vaginal fluid may increase the absorption of poorly water soluble drugs; however the same condition again responsible to remove the drug from the vaginal cavity and subsequent reduction of drug absorption. Further cervical mucus, a glycoprotein gel can possibly be exploited for bioadhesive drug delivery. However at the same time it may serve as a permeability barrier for different drug candidates²⁵. Again changes in the pH of vagina will alter degree of ionization of weak electrolytic drugs and affect the release profile of pH sensitive drugs²⁶.

Physicochemical Factors

The physicochemical properties of drugs and polymers like lipophilicity, ionization, molecular weight, surface charge and chemical nature can influence the vaginal drug absorption. Further the affinity and bindings of drug with other related component, introduced to prepare a 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 osmolarity²⁷. In consideration to permeability literature shows that lipophilic steroids like progesterone and estrone having better permeability than the hydrophilic one like hydrocortisone and testosterone²⁸. A study on vaginal absorption of polyvinyl alcohol suggested a molecular weight range above which compound will not absorbed and low molecular weight lipophilic drugs are preferably more as compare to high molecular weight lipophilic and hydrophilic one, vaginal mucosal surface is very specific in this respect. Experimental work till done on vaginal permeability suggest that the drugs intended

for vaginal deliver should have a certain degree of aqueous solubility.

Different Drug Delivery System for Vagina

History shows that starting from the beginning to till today selection of proper delivery system for vagina to deliver the drug for specific disease condition is an important factor in respect to rate and extent of drug absorption and therapeutic efficacy. Vaginal delivery is broadly categorized into two types: drug delivery for local action and drug delivery for systemic action. Delivery for local action are mainly intended to treat local fungal infection, antimicrobial therapy, spermicidal effect etc., and to achieved this goal delivery systems like solutions, foams, gels, creams are used. The present concept of vaginal delivery is bit changed not only in respect to improvement of conceptual local delivery of drugs but also a revolutionary focus on systemic delivery of drugs via vaginal route. Few years ago vaginal rings were mainly used for systemic effect of drugs, but today different novel concept like formulation based on polystyrene, formulation based on siliconelastomers, liposomal and submicron delivery devices, prolong release vaginal rings, cubic and environmental sensitive gel drug delivery systems, are capable to provide systemic effect for a prolong period of time. Hussain and Ahsan et al. concluded few formulation systems intended for vaginal delivery for different therapeutic agent are enlisted in table-1.

Jahnso and Masters show that the drug distribution and coverage of vaginal tissue varies considerably with the nature of delivery system²⁹. However quantitative measurement of drug after an intravaginal administration is a difficult task and also uncertain if administered formulation coated the whole organ. Chatterton et al. perform an interesting study introducing two radio labeled vaginal product, which describe the retention and distribution of 99m Tc-DTPA labeled vaginal cream (reference product) and a gel (experimental) dosages form, such study is use full for understanding comparative distribution of different formulated product²⁹. This portion of the article is mainly deals with the discussion different vaginal delivery system used till date. Although different vaginal product based on different delivery system are still under development, there are few that have been marketed for few years are summarized in the table -2.

Table- 1. Some of the experimented vaginal drug delivery system⁹ .

Therapeutic drug	Intended use	Dosage form	Animal model	Comments
Nonoxynol-9	Spermicide/topical contraceptive	Gel, Foam, Cream	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
Relaxin	Cervical ripening	Gel	Human	Decreased incidence of cesarean deliveries, reduced maternal-fetal morbidity
LHRH	Hormone dependent mammary tumors, fertility control	Suppository	Rat	Chronic administrations suppress secretion of ovarian steroids
Leuprolide	Ovulation inducing activity	Solution suppository, jelly	Rat	Activity increased by 5 times with addition of absorption enhancers
Insulin	Diabetes mellitus	Solution, gel	Rat, rabbit	Low bioavailability

Table – 2. Commonly used marketed vaginal product⁹ .

Therapeutic Drug (Brand Name)	Intended Use	Dosage Form	Comments	Company
Oxyquinoline sulphate, ricinoleic 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.
Etonogestrel, ethinyl estradiol (NuvaRing ®)	Contraceptive	Vaginal ring	Commonly reported adverse events are vaginitis, weight gain	Organon
Nonoxynol -9 (Conceptrol®)	Contraceptive	Vaginal gel		Advance Care Product
Progesterone	Infertility, secondary	Vaginal gel	Possible side effects	Fleet Laboratories

(Prochieve®)	amenorrhea		are breast pain, constipation	
Clotrimazole (Trivagizole®)	Anti-fungal	Cream	Minor skin irritation	Taro Pharmaceuticals
Metronidazole (Metrogel Vaginal®)	Bacterial vaginosis	Vaginal gel	Vaginal discharge.	3M Pharmaceuticals
Progesterone (Crinone®)	Infertility, secondary amenorrhea	Vaginal gel	Bioadhesive sustained release in nature.	Serono
Estradiol (Vagifem®)	Atropic vaginitis	Vaginal tablet	Mild allergic reaction.	Novo Nordisk
Dinoprostone (Prostin E2®)	Labour inducer	Vaginal gel		Pharmacia
Tioconazole (Trivagizole®)	Anti-fungal, vaginal Candida infection	Vaginal ointment	Possible side effects are swelling of face, lips, tongue.	Bristol Myers Squibb
Estradiol (Estring®)	Hormone therapy	Vaginal ring	Can increase the vaginal secretion	Pharmacia and Upjohn
Dinoprostone (Cervidil®)	Induction of labor	Suppositories	Side effect like abdominal cramp, diarrhea may occur.	Controlled Therapeutics

Creams and Gels

A number research work has been done on creams and gels as an intravaginal delivery system. They are mainly used for topical delivery of contraceptives and anti bacterial drugs. These delivery systems are messy to use, uncomfortable, may not provide an exact dose because of non-uniformity and leakage. Metronidazole and clindamycin vaginal creams for the treatment of bacterial vaginosis already proved them as efficacious as oral delivery. Lamont et al. performed a randomized controlled trial to evaluate the efficacy of clindamycin cream and found this cream was well tolerated and more efficacious than placebo.³⁰ Marcus E Brewster et al. reported a mucoadhesive cyclodextrin-based cream formulation of itraconazole shows effective therapeutic action on vaginal candidiasis³¹.

During past few years, considerable work has been done on development of different gel drug delivery systems which includes controlled release hydrogel delivery, pH sensitive gel delivery, thermo sensitive gel delivery systems etc. In hydrogel delivery basically hydrophilic polymers forms network structure by cross linkage via covalent bonding. A swelling controlled intravaginal gel of miconazole has been reported for anti fungal effect³². Again a 3% alginate gel of nonoxynol-9 has been investigated for intravaginal spermicidal activity and was found that the spermicidal activity and diffusion of the active agent changes with the pH and osmolarity of the formulation³³. Recently a gel microemulsion based

formulation of spermicide with anti HIV effect of zidovudine has been developed³⁴. literature shows that minocaprin hydrogel formulations possess potent microbicidal activity against HIV, HSV, *Chlamydia trachomatis* and *Neisseria gonorrhoea*, which is less cytotoxic than nonoxynol-9^{35,36}. Cellulose acetate phthalate (CAP) used the pharmaceutical industries as enteric coating agent but recent study focused that its having an potency to absorb and inactivate HIV-1, HSV and other STIs³⁷. Further utilizing this ability of CAP a potential anti-HIV vaginal gel formulation has been formulated that are under phase II clinical trials³⁸. 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 vaccine³⁹. Further oxytocin, dinoprostone 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 dinoprostone (prostaglandin E₂) vaginal gel versus vaginal tablet for the induction of labor shows significant difference in the labor out comes between two dosage forms⁴⁰. 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 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 same potentiality to induce labor and also safety and efficacy, as that of vaginal administration⁴¹, where as a study by shetty et al. shows that vaginal administration of drug were more efficacious than the oral route⁴². Recently Chang et al. conducted a study to determined 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 polycarbophil⁴³. As per Edsman et al. gels are one of the most commonly studied mucoadhesive formulations for vaginal drug delivery.

Tablets and Suppositories

A large number of intravaginal delivery systems are also available in the form of tablets and suppositories. Some authors use the terms pessaries and suppositories interchangeably and consider vaginal tablet as a separate dosage form. These formulations are designed to melt in vaginal cavity and release the active constituent over prolong period of time. Suppository systems are most commonly used to administer drugs like dehydroepiandrosterone sulphate for ripening effect on uterine cervix, miconazole for vaginal candidiasis and progesterone for hormonal replacement therapy. Normal vaginal tablets contain similar components as like conventional oral tablets, they are easy to manufacture and insertion. Drugs that are administered as vaginal tablets include itraconazole, clotrimazole, metronidazole and prostaglandins. Mucoadhesive polymers are sometimes used in vaginal tablet formulation to increase the vaginal residence time. Recently Mohd Afftab Alam 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 system⁴³. 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 system⁴⁴. Amal Ei-Kamel et al. reported a chitosan and sodium alginate based bioadhesive vaginal tablet of metronidazole⁴⁵. 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 formulation⁴⁶. Literature shows that presence of hydrophobic and release retarding materials may decrease the

absorption of a drug from a vaginal formulation and too hydrophobic drugs may not be suitable for vaginal tablets. Further presence of penetration enhancers such as surfactants, bile salts can significantly enhance absorption.

Vaginal Ring

Vaginal rings are circular ring type drug delivery devices designed to release drug in a controlled release fashion after insertion in the vagina. This type of device having several advantages like, it can be controlled by the user, does not interfere with coitus and allows continuous delivery of microbicide compounds. They are 5.5 cm in diameter with a circular cross section diameter of 4-9 mm, where drugs are homogeneously dispersed. Drugs at the surface of the ring release faster than the drug in the inner layer. The key challenge behind the development of this type of device is finding the optimum dose that will deliver the least amount of drug necessary to ensure protection. To obtain constant release of drug from vaginal ring sandwich or reservoir types of system have been developed. Sandwich type devices consist of a narrow drug containing layer located below the surface of the ring and positioned between a non-medicated central core and a non-medicated outer band. In reservoir type of rings, drugs are dispersed in a central core, which is then encapsulated by a drug free layer. The materials introduced to fabricate vaginal ring are mainly polymeric in nature. As per literature most commonly used polymers for vaginal ring are ploy (dimethylsiloxane) or silicon devices, other elastomeric polymers such as ethylene vinyl acetate and styrene butadiene block copolymer have been tested in recent years⁴⁷. 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 resistance⁴⁹. Vaginal rings mainly used for contraceptive and hormonal replacement therapy. For most contraceptive application the ring is placed in vagina for 21 days followed by a week of ring free period. Nuvaring is one of the example of contraceptive ring available in US market⁵⁰. Further Femring and Estring are the example of vaginal ring intended for hormonal replacement therapy, release estrogen. Literature reported that dapivurine, which is also known as TMC120, is a potent non-nucleoside reverse transcriptase inhibitor that is the only vaginal ring system used as an intravaginal microbicide delivery system for preventing the transmission of STIs and HIV⁵¹.

Table no -3, Status of vaginal formulations in clinical trial stage ⁶².

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 BufferGel® as a Vaginal Contraceptive	Phases II and III	Compare BufferGel® to Gynol II®, a currently available contraceptive ge	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

Bioadhesive Delivery System

Most of the conventional vaginal formulation associated with several disadvantages of low retention to the vaginal epithelium, leakage and messiness, thereby causing poor patient compliance. To circumvent these challenges bioadhesive vaginal drug delivery system are being propagated. Bioadhesive polymers that have been most commonly used for intravaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid. The first bioadhesive systems for vaginal drug delivery were in the form of tablet for the delivery of bleomycin, an anticancer agent. A bioadhesive polycarbophil gel, Replens®, is available in the market, which used to retain moisture and lubricate vagina for 2-3 days and maintain a healthy condition⁵². Attempt has also been made to delivery of microbicides using bioadhesive microparticulate vaginal 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 effect⁵³. A mucoadhesive controlled release drug delivery system for nonoxynol-9, a spermicidal agent, has been reported, which contain various levels of nonoxynol-9 and EDTA, a chelating agent, were formulated using carbopol 934P polymer^{54,55}. A new mucoadhesive vaginal dosage form for the antimycotic agent, clotrimazole, was developed by incorporating bioadhesive polymers like polycarbophil, hydroxypropylmethylcellulose and hyaluronic sodium salt into suppositories made up of semi synthetic solid tri glycerides⁵⁶.

Few Current Intravaginal Drug Delivery Approaches

This part of the article is mainly focused on very recent advancement and upcoming drug delivery systems. SPL2008 (viva Gel™) is a dendrimer-based microbicide delivery system, in which dendrimer is used not as a carrier but as an active ingredient⁵⁷. SPL7013 emerged as most promising dendrimer after preclinical studies, which binds and blocks HIV-1 thereby preventing STIs, including HIV and genital herpes, and has been formulated as a gel that is under phase-I clinical trail⁵⁸. Development of monoclonal human antibodies in the form of microbicidal gel for protecting genital skin and epithelia against infection by topical immunization is one of the major achievement, this type of monoclonal synthetic antibodies can be directly applied directly to the genital skin and epithelia for protection from HIV and other STIs pathogens⁵⁹. PHI-444 a rationally designed novel thiophen-thiourea basically a non nucleoside reverse transcriptase inhibitor with potent activity against HIV-1, formulated as intravaginal gel formulation and found safe in rabbits. Further the molecular condom is a recently developed anti-HIV vaginal gel, which release anti-HIV bioactives upon contract with the serum during sexual intercourse. It is basically a hydrogel sensitive to body temperature and pH, and serves as a smart semen-triggered vaginal microbicide delivery vehicle, design to protect women and unborn or nursing child from HIV⁶⁰. A study has been conducted on short interfering RNA (siRNA) as potential liposomal microbicide delivery, where in-vitro test result shows that siRNAs are absorbed throughout the vaginal tissue. This delivery system

was design to target messenger RNA by complementary base pairing and splits it in a selective fashion, thus halting protein expression or viral replication⁶¹. Some of the recently developed microbicidal delivery systems, on which experiments are carried out at clinical trial in different level, are tabulated in table -3.

Conclusions

Although a number of research works has been done on vaginal drug delivery system but till a huge task is remain to be cover. Vagina as a route of drug delivery is having several critical clinical obstacles, which became a challenge to design appropriate drug delivery system. In few aspect of macromolecular drug delivery for vagina either locally or systemic shows significant promise as well as acceptance within the female

population. Among the several vaginal delivery systems, vaginal gels, advance prolong action vaginal rings and recently novel bioadhesive vaginal delivery systems are already prove there potentiality. With the increasing number of novel polymers, rationally applied drug design in each year will definitely move vaginal delivery system one step ahead in way of success. Based on the research performances done till date, it can be conclude that the concept of vaginal drug delivery going to play a vital role in order to protect from the major pandemic disease of the world, HIV. In this review we summarized the continues interest and the current researches in this field, further a huge amount of work is required to be done in order to established optimized several vaginal delivery systems and allow the excellence for clinical outcome.

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