IJPSR (2021), Volume 13, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 March 2021; received in revised form, 14 June 2021; accepted, 21 June 2021; published 01 February 2022

THERAPEUTIC CARRIERS FOR THE VAGINAL DELIVERY OF ANTI-HIV DRUG

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Keywords:

Human immunodeficiency Virus, retroviral infections, Vaginal delivery, Novel drug delivery.

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ABSTRACT: HIV is a pandemic disease that is rapidly spreading across the world. The current review's objective is to present how comprehensive various advanced anti-HIV drug delivery systems are. The use of a new drug delivery system helps in overcoming the challenges of dosage form growth, such as drug instability, insolubility, and restricted entrapment. Several delivery routes for ARV therapy have been identified, including trans dermal, mucosal (vaginal, rectal, buccal, *etc*.) and lymphatic delivery, utilizing novel systems such as nanoparticles, vesicular systems (liposomes, niosomes, ethosomes, emulsomes), micellar assemblies and so on. This review examines the potential of novel drug delivery systems for the prevention, treatment of retroviral infections, approaches and applications of novel drug delivery systems for Anti-HIV agents.

INTRODUCTION: The Acquired Immune Deficiency Syndrome (AIDS) and associated infections caused by the human immunodeficiency virus (HIV) have been described as one of the dreadful diseases that pose troubling challenges to community health around the world especially in sub-Saharan Africa [1]. According to global estimates, there are more than 33.2 million people living with this infection. According to predictions from Indian health organizations, India will have about 6-7 million HIV-positive patients. 2.5 million people were newly infected in 2007, [2].1 million died of AIDS, and 2.5 million people in.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(2).543-58

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(2).543-58

India was diagnosed with HIV (2-3 million in 2006). HIV infection was converted from a foetal to a controllable chronic infectious disease as a result of treatments such as AIDS educational resources and counselling, as well as antiretroviral therapy (ART) [2]. HIV-1 and HIV-2, as well as their sub-species, are the two recognized species of human immunodeficiency virus. HIV-1 infections are common in the world, while HIV-2 infections are predominant in West Africa and take longer to evolve into immunodeficiency syndrome [3, 4].

Vaginal Anatomy, Histology and Physiology: The vaginal canal is a female reproductive tract organ. It's a distensible muscular tube that passes from the external vaginal orifice to the cervix in a posterosuperior position.

Anatomical Structure: The vaginal canal is a fibro muscular tube with anterior and posterior walls that are usually collapsed and in contact. The vagina does not have a round tunnel shape. It looks

more like a "H" lying on its side in the transverse plane. The vagina wraps the cervix at its upper end, forming two domes (fornices or vaults): an anterior and a (deeper) posterior one. After intravaginal ejaculation, the posterior fornix acts as a natural reservoir for semen. In the next 20-30 min, the semen stored in the fornix liquefies, allowing for easier permeation through the cervical canal [5].

Anatomical Position: The vagina is closely related to many of the organs in the pelvic region.

- Anterior - Bladder and urethra.
- Posterior - Rectouterine pouch, rectum and anal canal.
- Lateral- Ureters and levator ani muscle.

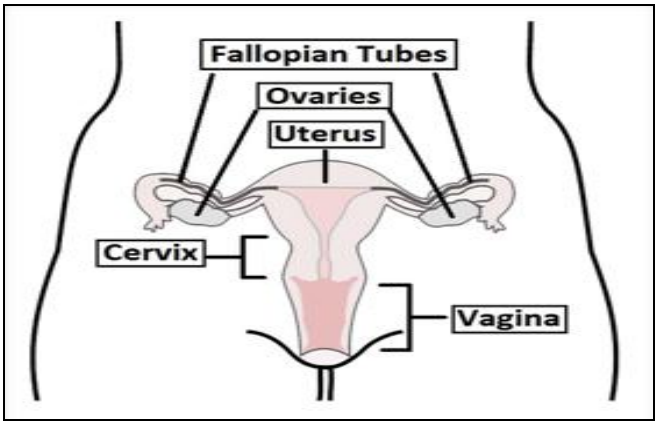

FIG. 1: OVERVIEW OF THE FEMALE REPRODUCTIVE TRACT

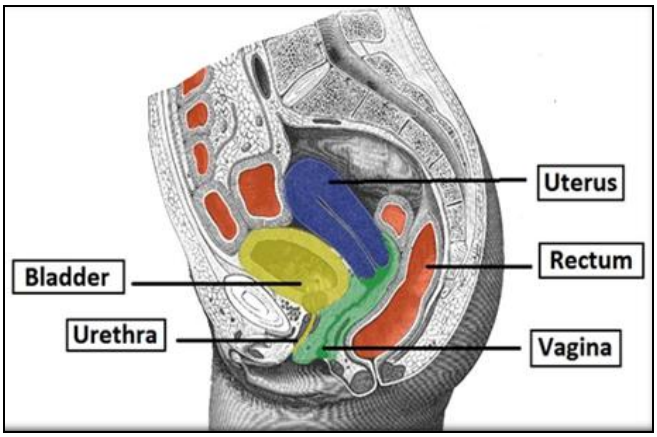

FIG. 2: SAGITTAL SECTION OF THE FEMALE PELVIS, SHOWING THE ANATOMICAL RELATIONS OF THE VAGINA

Histology of the Vagina: The vagina is composed of four histological layers (internal to external):

Stratified Squamous Epithelium: This layer provides protection and is lubricated by cervical mucus (the vagina itself does not contain any glands).

Elastic Lamina Propria: A dense connective tissue layer that projects papillae into the overlying epithelium. The larger veins are located here.

Fibromuscular Layer: Comprising two layers of smooth muscle; an inner circular and an outer longitudinal layer.

Adventitia: A fibrous layer, which provides additional strength to the vagina whilst also binding it to surrounding structures [6].

Physiology: It has several roles within the female reproductive system:

- Sexual intercourse - Receives the penis and ejaculate, assisting in its transport to the uterus.
- Childbirth - Expands to provide a channel for delivery of a newborn from the uterus.
- Menstruation-Serves as a canal for menstrual fluid and tissue to leave the body [7].

Vaginal Transmission of HIV: Male-to-female sexual transmission accounts for the vast majority of new HIV infections in women. HIV is passed from an infected male's sperm to an uninfected female partner during such intercourse and overcomes some of the host's protective barriers. Mucus, epithelial layers, secreted neutralizing antibodies, and protective proteins (e.g., -defensins, immunoglobulins, complement, antimicrobial peptides, lysozyme, and lactoferrin) are examples of host barriers against these microbes in the genital tract [8].

Semen as A Vehicle for HIV-1 Transmission: Since the discovery of HIV-1 in genital secretions, several studies have looked into the relationship between viral concentrations in these fluids and the risk of transmission, finding that a higher viral concentration in genital secretions raises the risk of HIV-1 sexual transmission. The level of seminal HIV-1 varies depending on the stage of infection: for example, in the acute phase of infection, more viral particles are found in HIV-1-infected men's sperm and the risk of HIV transmission ranges

from 8 cases per 1000 vaginal coital actions to 1-2 cases per 1,000 in the chronic phase. Antiviral therapy lowers the viral load in the seminal vesicle, lowering the risk of transmission. For years, scientists have discussed the source of HIV-1 in sperm. Since genetic variations between viruses isolated from blood and semen were discovered, blood does not appear to be the only source of seminal HIV-1.

Some genetic signatures, in particular, are only found in seminal HIV-1 (*e.g.,* specific glycosylation patterns in the viral envelope gp120) [9]. Other HIV-1 genetic tests showed that seminal HIV-1 is mainly originated from male genital tract tissues. Male genital organs, such as the testis, epididymis, prostate, and seminal vesicles, were infected by SIV in both acute and chronic phases of infection in macaques, indicating that they may be the source of HIV-1 present in semen.

Furthermore, cells that can be productively infected by HIV-1, such as CD4+ CCR5+ T cells and macrophages, were present in cultures of human testis and prostate. Anderson *et al.* suggested that viral populations in semen originate from several origins, including direct import of virus from blood and oligoclonal amplification within the male genital tract, based on phylogenetic analysis of viral sequences in blood and semen. The presence of the virus in the ejaculate is not prevented by vasectomy, suggesting that most cell-free HIV in seminal plasma originates distally from the vas deferens. As a result, seminal HIV-1 is made up of a large group of viruses formed by sperm-producing organs and blood [10].

Semen Affects HIV Acquisition: HIV-1, which is borne by sperm, is deposited in the vaginal mucosa during heterosexual intercourse. Semen is more than just an HIV-1 carrier because it includes a range of biological factors that can support or inhibit HIV-1 transmission. Semen, for example, neutralizes the acidic cervical mucus, allowing HIV-1 to disperse that would otherwise be stuck in the mucus. In addition, semen has the potential to change the chemical and physical properties of female genital mucus. Semen, for example, comprises amyloid fibrils derived from prostatic alkaline phosphatase (SEVI) and semenogelins (SEM1 & SEM2), both of which facilitate viral attachment to target cells, thereby enhancing HIV-1 transmission. These fibrils improve cell-free HIV-1 infectivity but do not affect cell-associated HIV-1 infectivity. Semen also produces complement system inhibitors like CD59, which could help viruses evade complement-mediated virucidal activity.

Seminal Free and Cell-Associated Virus in the Establishment of HIV-1 Infection: Most HIV-1 or SIV transmission studies used cell-free viruses. The body of information about the role of cell-associated virus in HIV-1 transmission is growing. Since HIV-1 can be briefly adsorbed on the cell surface and then released as a free virus, it can be difficult to differentiate between virus deposited on the vaginal mucosa in cell-free or cell-associated forms. Virus adsorbed to seminal cells can only be considered cell-associated if it persists on the cell surface (*e.g.,* spermatozoa) during contact with female genital epithelia [11].

The definition of infection spread by pathogen-carrying cells (also known as "Trojan Horses") predates the detection of HIV as the cause of AIDS. After atraumatic inoculation in the vaginal lumen, two separate groups discovered *in-vivo* proof that mouse spleen mononuclear cells can cross the mouse vaginal epithelium. Furthermore, HIV-infected human cells have been shown to migrate transepithelial and spread infection in hu-SCID mice. Similarly, intravaginal inoculation of SIV-infected cells resulted in chronic infection of exposed animals in a non-human primate model.

In humans, a longitudinal study showed that the HIV-1 genotype found in women with acute infection matched the viruses incorporated in their infected male partners' seminal cells, indicating that HIV originated from infected cells found in semen, mostly lymphocytes, and macrophages.

This is consistent with studies showing that intravaginal inoculation of a semen simulant containing 111 In-radiolabeled autologous leukocytes and 99mTc-radiolabeled nanoparticles allows both labelled components to migrate in the human cervical tract. As a result, it appears that both free virus and infected cells will communicate with cervicovaginal tissue, transmitting infection during heterosexual intercourse [12].

Methodologies to Prevent HIV Transmission by Vaginal Route: Unintended pregnancies account for about 41% of all pregnancies worldwide, with rates much higher in South America (64%) and Southern Africa (59%) than in North America (48%). Increased contraception usage to avoid unintended pregnancies is a cost-effective approach with multiple personal, familial and societal benefits, including lower maternal and infant mortality, as well as increased educational and economic gender equality. Contraception is also the most cost-effective method for reducing the burden of HIV transmission from mother to child among HIV-positive women who want to avoid unintended pregnancy. Unfortunately, some of the countries with the highest rates of HIV also have the lowest rates of contraception usage and the highest rates of unintended pregnancies [13].

Prevention of new HIV infections and unintended pregnancies is crucial to improving health, preventing mother-to-child transmission, and reducing infant and maternal morbidity and mortality, according to the World Health Organization (WHO), the United Nations, and other global public health organizations. Improving contraception access and use for women living with or at high risk of HIV infection is therefore a public health priority [14].

Contraceptive Efficacy of Various Methods: Although condoms are the only form of contraception that can minimize the risk of sexually transmitted infections (STIs), such as HIV, they have a high failure rate for pregnancy prevention due to poor adherence, with a typical usage rate of 18-21% during the first year of use. Furthermore, despite three decades of condom promotion for HIV prevention, consistent and accurate condom use is reported to be uncommon among high-risk individuals in HIV-endemic regions.

Hormonal contraceptive methods are more successful than condoms for preventing pregnancy, with a typical-use contraceptive failure rate of about 9% for combined hormonal contraception (oral contraceptive pills, patch, or ring), 6% for injectable methods [depot medroxyprogesterone acetate (DMPA) or norethisterone enanthate (NET-EN)], and less than 1% for contraceptive methods (IUDs) [15].

The diaphragm, cervical cap and spermicides are nonhormonal contraceptives with a lower contraceptive efficacy (12-28% failure rate with normal use). Diaphragms have been linked to an increased risk of sexual HIV acquisition when used regularly, and certain types of spermicide, such as nonoxynol-9, have been linked to an increased risk of sexual HIV acquisition when used frequently. Fertility awareness methods, such as the symptothermal approach, can be extremely successful when used correctly, but failure rates for certain types of fertility awareness methods are as high as 24%.

Surgical sterilization, which involves bilateral tubal ligation for women and vasectomy for men, is an exceptionally successful contraceptive method with a typical-use failure rate of less than 1% however, access to these procedures may be limited in low-resource environments and sterilization is not suitable for pregnancy spacing due to its lack of reversibility [16].

Hormonal Contraceptive Methods and HIV Acquisition Risk: Despite their high global uptake and excellent contraceptive efficacy, there is increasing concern that hormonal contraception, especially progestogen-only injectables (such as DMPA or NET-EN), can increase the risk of HIV acquisition in uninfected women or female-to-male HIV transmission when used by HIV-positive women. These threats, if confirmed, would have major consequences for the person and population's health. The risk of developing simian immunodeficiency virus (SIV) in rhesus macaques increased several-fold after exposure to large doses of DMPA, according to studies in nonhuman primates [17].

In human studies, the possible risk of HIV acquisition associated with injectable contraception has not been reliably observed, with some studies documenting no association with DMPA and others reporting an increased risk of HIV acquisition. Study nature, population, sample size, contraceptive methods tested, dosage, contraceptive adherence, analytic methods used, and rate of method discontinuation all contribute to the challenge of interpreting findings through these observational studies, restricting the conclusions that can be drawn [18].

Potential Biologic Mechanisms for Increased HIV Acquisition and Transmission Risk Associated with Certain Hormonal Contraceptive Methods:

Acquisition of HIV Infection is A Multifaceted Process of Virus-host Interactions: In addition to the transmitter's plasma viremia, factors that increase the partner's vulnerability to HIV infection include the involvement of STIs, mucosal micro-abrasions, and secreted immune factors-all of which affect local mucosal immunity, the defensive integrity of the genital tract epithelial barrier and the activation status of HIV target cells involved in the early stages of the infection [19]. According to evidence, female sex hormones can influence the robust nature and functional ability of innate and adaptive immune responses. Estradiol and progesterone's immunoregulatory effects change the immunologic milieu and immune cell composition in the female genital tract (FGT), providing a favourable climate for fertilization and pregnancy [20].

Factors That Influence Contraceptive Choice May Impact HIV Risk: Several studies have looked into the factors that affect seronegative women's contraceptive choice and usage. The majority of adult HIV-seropositive women studies have been carried out in international settings, mainly in Africa, with just a few studies from the United States. These studies emphasize the importance of healthcare coverage and women's concerns regarding contraceptive side effects or possible interactions with ARVs, the convenience of barrier contraceptive methods, and their desire to have children as determinants of contraceptive method usage in HIV-positive women.

Furthermore, contraceptive use may vary depending on the type of partner; for example, contraceptive use was more common among women reporting recent sexual experiences with casual partners in a cohort of French women living with HIV [21]. Any behavioural variations between women who use hormonal contraceptives and other women may be attributed to a woman's underlying HIV infection danger. While observational studies may attempt to test for these factors, residual (in addition to unmeasured), confounding may occur, further complicating our understanding of the effect of hormonal contraceptive methods on HIV danger. Unprotected sexual experiences, for example, may change as a result of contraceptive use, altering the risks of HIV and other STIs to uninfected partners. Furthermore, unprotected coitus associated with STI and semen exposure can alter the inflammatory environment in the genital tract, raising the risk of HIV transmission. *In-vitro* studies have shown that whole semen can double HIV infectivity, increase Langerhans cell recruitment to the vaginal mucosa, and upregulate the expression of pro-inflammatory cytokines in the female genital tract. HIV shedding and transmission have also been related to co-infections with STIs and other genital infections. Micro-ulcers or local recruitment of activated immune cells to the genital tract may blame the increased risk. Consequently, irregular condom usage, which is difficult to account for in observational studies, can alter HIV susceptibility and infectivity, potentially altering the relationship between contraception and HIV acquisition and transmission [22, 23].

The Influence of Combination Antiretroviral Therapy: The use of combination antiretroviral therapy (ART) decreases HIV transmission and clinical disease progression. Plasma viral load (VL) has been shown to be a successful indicator of heterosexual transmission, and ART reduces viral load in the blood and the genital tract. According to the results of the HIV Prevention Trials Network (HPTN) 052 study, people living with HIV who began antiretroviral therapy (ART) when their CD4 counts were >350 cells/l were 96% less likely to transmit HIV to uninfected partners than those who delayed starting ART. The key cause of recurrent plasma viremia is poor adherence to antiretroviral therapy (ART) [24, 29]. Adherence is more likely to be low in some at-risk populations (e.g., teenagers and young adults).

Several studies have found observable HIV in the cervicovaginal fluid of women on Sculpture, even when the woman's plasma viral load is undetectable. As a result, it's important to recognize possible modulators of viral load in mucosal compartments. The effect of antiretroviral therapy (ART) on genital HIV-1 RNA shedding in the context of hormonal contraceptive use is also significant, as ART may reduce the risk of HIV transmission associated with hormonal contraceptives. Although there is conflicting

evidence regarding a correlation between DMPA use and genital HIV-1 RNA shedding in HIV-positive women, a recent study in Kenya among women on ART found no link between DMPA use and plasma or cervical HIV-1 RNA. According to this report, DMPA is unlikely to raise the risk of HIV transmission in women who are taking antiretroviral therapy [30, 34].

Dosage Forms: The scientific community and the pharmaceutical industry are currently very interested in using different mucosal routes to deliver poorly absorbed drugs after oral administration. Despite its potential as a noninvasive route of drug administration, the human vagina remains a largely unexplored route of drug delivery, based on the number of research papers published in pharmaceutical journals over the last decade. The vagina is an ideal route of drug delivery for both systemic and local effects due to its dense network of blood vessels [35]. The key advantages of vaginal drug delivery over traditional drug delivery are the ability to bypass first-pass metabolism, ease of administration, and high permeability for low molecular weight drugs. However, many disadvantages must be discussed during the production of a vaginal formulation, including cultural sensitivity, personal hygiene, gender specificity, local discomfort, and the effect of sexual intercourse. Changes in the thickness of the vaginal epithelium often indicate major variability in the rate and degree of absorption of vaginally administered drugs [36].

Physicochemical Properties o Drugs: Vaginal drug absorption is affected by physicochemical properties such as molecular weight, lipophilicity, ionization, surface charge, and chemical composition. Straight chain aliphatic alcohols, for example, increase vaginal permeability in a chain length-dependent manner. Similarly, lipophilic steroids like progesterone and estrone have much higher vaginal permeability than hydrophilic steroids like hydrocortisone and testosterone [37]. Low molecular weight lipophilic drugs, on the other hand, are thought to be absorbed more readily than large molecular weight lipophilic or hydrophilic drugs. The molecular weight cut off above which compounds are not absorbed may be higher for the vagina than for other mucosal surfaces, according to a report on vaginal absorption of polyvinyl alcohol. Since vaginal fluid contains a considerable amount of water, any drug intended for vaginal delivery must contain a certain amount of water.

The degree to which anything is soluble in water. In reality, there is a scarcity of data on the human vaginal permeability of drugs with various physicochemical properties; far further research is required on the effects of physicochemical drug parameters on vaginal absorption [38].

Drug Delivery Systems for Vaginal Administration: A vaginal ring has recently been developed for hormone replacement and contraception. Drug absorption, distribution, and residence time in the vagina may differ depending on the drug delivery method or formulations used. In fact, early studies in this field showed that the drug distribution and coverage of vaginal tissue differ greatly depending on the delivery mechanism, with solution, suspension, and foam proving to be superior to tablet dosage types. A vaginal drug delivery device with a local effect can, in principle, spread equally across the vaginal cavity. If a local or topical effect is necessary, the option of vaginal drug administration should be based on the applicability of the intended effect. A semi-solid or quickly dissolving solid system would be needed for a local effect to occur. A bioadhesive dosage type or an intravaginal ring system would be preferred for a topical effect. However, it has been difficult to quantify drug delivery after intravaginal administration, and it is also unclear if the administered formulation coated the entire organ. In this regard, a fascinating help. Vaginal delivery may be designed to administer drugs through an applicator or explicitly designed intravaginal administration systems [39].

Advantages of Vaginal Drug Delivery System: While vaginal administration is the preferred and targeted route for new drugs and dosage types, it can be used as an alternative in certain therapeutic cases: The act of taking medication orally can cause emesis, causing the drug to be vomited before it is absorbed, which can cause nausea and vomiting. Certain medications can cause stomach and small intestine irritation, which can be avoided. Partially preventing hepatic first-pass removal of high-clearance drugs is possible.

Some drugs are shielded from enzymatic degradation by avoiding interaction with the digestive fluid. By eliminating the medication type, such as vaginal rings, drug distribution can be prevented. Drugs traditionally only given to parents can now be given vaginally, either alone or in conjunction with absorption-enhancing 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 approaches.
- Self-medication is possible.

Limitations of Vaginal Drug Delivery Systems:

- 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 undergarments [40].

Classification of Intra-Vaginal Drug Delivery System:

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

Vaginal Rings: Vaginal rings are spherical ring-shaped drug delivery devices that are implanted into the vagina and release the drug in a controlled manner. Vaginal rings have the benefits of being user regulated, not interfering with cation, not requiring regular pill intake and enabling consistent delivery of low dose steroids. The ring is implanted in the vagina and measures approximately 5.5 cm in diameter with a circular cross-section diameter of 4-9 mm. The drug is homogeneously distributed inside a polymeric ring in clear vaginal rings. The drug on the ring's surface is released quicker than the drug in the ring's inner layer. Drugs in the outermost layer may often induce an initial burst release. Sandwich or reservoir-style rings have been developed to obtain a constant release of drug from a vaginal ring. Sandwich devices have a thin drug-containing layer under the ring's surface, sandwiched between a non-medicated central core and a non-medicated outer band. Drugs are dispersed in a concentrated center in reservoir-style rings, which are then encapsulated by a drug-free polymer sheet. It is possible to have several cores of different drugs in a single ring, allowing several drugs to be administered from the same unit [41].

Changing the core diameter or thickness of the non-medicated coating will alter the rate of drug release. The material used to make vaginal rings is typically polymeric. Although other elastomeric polymers such as ethylene-vinyl acetate and styrene-butadiene block copolymer have been tested in recent years, much of the vaginal ring literature relates to widely used polymer, poly (dimethylsiloxane), or silicone products, although other elastomeric polymers such as ethylene-vinyl acetate and styrene-butadiene block copolymer have been tested in recent years. Increased flexibility, enhanced optical properties, increased adhesion, and increased impact and puncture resistance are all benefits of adding vinyl acetate units to polyethylene [42].

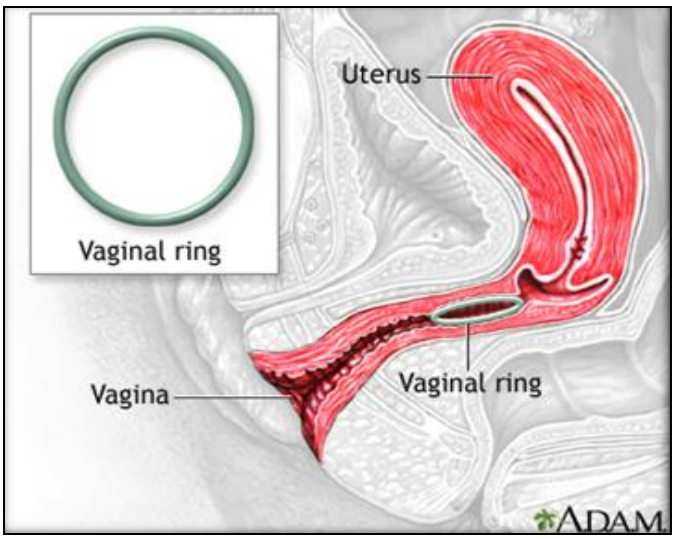

FIG. 3: VAGINAL RING

FIG. 4: VAGINAL TABLET

TABLE 1: COMPONENTS

Components	Uses
Microcrystalline cellulose	Diluent
Anhydrous lactose	Diluent
Crossarmellose	Binding agent
Magnesium stearate	Lubricant

Furthermore, ethylene-vinyl acetate rings have a high clinical acceptability. The acceptability percent among the subjects participating in the analysis was 91 percent when determining the tolerability of an ethylene-vinyl acetate no medicated vaginal ring with a diameter of 54 mm. The ring was expected to stay in for 21 days after it was placed in, allowing for temporary removal during coition. The majority of the women felt the ring was easier to put on and take off. During the study period, no adverse effects were found in the control sample. Contraception and hormone replacement therapy are also performed with vaginal rings.

Most contraceptive rings are put in the vaginal canal for 21 days, followed by a week without wearing them. In the United States, Nuva Ring is the only combined contraceptive vaginal ring available. Nuva Ring is a lightweight, transparent contraceptive vaginal ring that contains etonogestrel and ethinyl estradiol as active ingredients. Over the course of three weeks, the ring releases 120 mg of etonogestrel and 15 mg of ethinyl estradiol every day. Nuva Ring is an efficient contraceptive ring with strong cycle regulation and consumer acceptability, according to clinical studies. FemringR and EstringR are oestrogen releasing rings that are used for oestrogen therapy. FemringR is a silicone elastomer that contains acetate derived from estradiol and is inserted in the vaginal canal once per trimester. After being released from the delivery system, estradiol acetate is hydrolyzed to estradiol. Estring R is made of silicone polymers and releases 7.5 mg of estradiol per day when implanted in the vaginal canal [43].

Vaginal Tablet: The tablet for vaginal delivery is manufactured either by wet granulation or direct compression.

Vaginal Powder: Vaginal powder is made by heating hydroxypropyl cellulose and dissolving it in water. The bisphosphonate is added after the mixture has been slightly cooled. The mixture is lyophilized before being used.

Vaginal Capsule: Filling the prepared powder into capsules is how vaginal capsules are made. While the invention has been defined in terms of many preferred embodiments, a professional artist can realize that various changes, substitutions, omissions, and additions can be made without departing from the spirit of the invention. As a result, the scope of the present invention is supposed to be limited solely by the scope of the following claims.

Vaginal Ointment: An oil and an aqueous process are used in the invention's vaginal ointment. The medication chosen from the group of compounds consisting of alendronate, clodronate, tiludronate, pamidronate, etidronate, ibandronate, neridronate, residronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate, zoledronate Both phases have been extensively combined.

Vaginal Creams and Gels: Topical contraceptives and antibacterial drugs are administered *via* creams and gels. When these vaginal dosage types leak into the undergarments, they are messy to apply, painful, and often humiliating. Furthermore, due to nonuniform delivery and leakage, creams and gels do not have an exact dosage. Acceptability and viability are two desirable characteristics of a vaginally applied microbicide cream or gel. They must be easy to use, non-toxic and gentle on the mucus membrane. Metronidazole and clindamycin vaginal cream have been found to be almost as effective as orally administered medications in treating bacterial vaginosis.

Lamont *et al*., performed a randomised, placebo-controlled 3-day course trial in pregnant women during the second trimester to determine the effectiveness of an antibacterial vaginal cream in the treatment of bacterial vaginosis. Clindamycin vaginal cream was found to be well-tolerated and more effective than placebo in the procedure. Present efforts aim to develop topical intravaginal formulations of anti-HIV agents or microbicides to minimize mucosal and perinatal virus transmission in the absence of an appropriate prophylactic anti-HIV vaccine or therapy. The theory of emulsion or hydrogel-based drug delivery could be used in vaginal creams and gels.

The development of hydrogel-controlled release drug delivery systems has gotten a lot of attention in recent years. When put in an aqueous environment, these hydrogels swell and hold significant quantities of water in their swollen form, releasing the drug in a regulated manner. It has been confirmed that a swelling-controlled release hydrogel delivery system for intravaginal administration of miconazole, an antifungal medication, has been developed. Hydrogels are hydrophilic polymers that have been covalently linked together. The delivery of intravaginal spermicide was examined using a 3% alginate gel of nonoxyno [l, 9]. The spermicidal activity and diffusion of the agent were found to change with the pH and osmolarity of the formulation in the sample. Gel-micro emulsions have recently been suggested as a nontoxic vaginal formulation.

It has been developed a gel micro emulsion-based formulation of a spermicide with anti-HIV effect, a vinyl phosphate derivative of zidovudine. In a rabbit model, multiple intravaginal treatments of this drug as a microemulsion gel formulation caused no harm to the vaginal epithelium. The vaginal gel has also been used to administer vaccines intravaginally. When cholera vaccine was administered intravaginally, it elicited a stronger mucous response in the female genital tract than when the vaccine was given orally. As a vaginal gel, antibacterial agents and drugs for cervical ripening and induction of labour are also available. Cervical ripening and induction of labour medications include oxytocin, dinoprostone, and misoprostol. Induction of labour with dinoprostone (prostaglandin E2) vaginal gel versus vaginal tablet was studied recently. The researchers used a retrospective approach to compare labour results between women who received dinoprostone vaginal gel (1-2 mg) for three months and women who received dinoprostone vaginal tablets (3 mg) for three months. According to the authors, there were no statistically significant variations in labour outcomes between dinoprostone vaginal gel and tablet used in the induction of labour. However, the authors did not compare the protection of the two dosage types in their report. Another research compared the effectiveness and safety of dinoprostone vaginal inserts with vaginal tablets. Women who wanted labour induction were given a 10 mg dinoprostone vaginal insert or a 3 mg at dinoprostone tablet twice six h intervals at random.

The incidence of uterine hyperstimulation, irregular foetal heart rate patterns, use of h-2 adrenergic medications, and foetal outcome were used to assess the complications for the two dosage types. The time between the induction agent being inserted and the initiation of normal uterine contractions was classed identical in both. The removal of the insert was enough to avoid the hyperstimulation in seven of the eight patients in the community who were receiving the insert and experiencing uterine hyperstimulation. Eight out of nine subjects in the tablet group, on the other hand, needed medical intervention to stop the hyperstimulation.

The efficacy of vaginal misoprostol and dinoprostone vaginal gel for labour induction was compared in this interesting review. The key outcome indicators were the need for oxytocin during childbirth, the need for analgesia, the mode of delivery, the time from induction to delivery, and the neonatal outcome. When compared to the dinoprostone administered group, the misoprostol administered group had a lower need for oxytocin in labour but a slightly shorter time for induction to delivery.

However, there were no variations in the need for analgesia, delivery mode, or neonatal outcome between the two cohorts. Vaginal misoprostol administration was found to be more effective than prostaglandin F2-a gel and dinoprostone suppository in a recent randomized controlled trial involving dinoprostone suppository [44].

FIG. 5A: VAGINAL GEL

However, both misoprostol and dinoprostone suppositories demonstrated a lower need for oxytocin and a shorter labour time compared to PGF2-a gel. The intravaginal administration of misoprostol has been extensively researched since its introduction in 1993 for labour induction. Several studies comparing the efficacy of oral and vaginal misoprostol delivery have recently been published in the literature. The dose of misoprostol required for oral delivery is normally four times that required for intravaginal delivery. However, there have been some contradictory reports on the effectiveness of the misoprostol administration route.

For example, Hall *et al.* found that oral misoprostol could induce labour as safely and effectively as vaginal misoprostol, while a study found that vaginal misoprostol was more effective than oral misoprostol, despite the fact that the oral (100 mg) and vaginal (25 mg) doses, as well as the drug administration intervals, were the same in both studies. Misoprostol doses for oral delivery are usually four times higher than those for intravaginal delivery. However, there have been several conflicting studies about the efficacy of misoprostol administration. For example, despite the fact that the oral (100 mg) and vaginal (25 mg) doses, as well as the drug administration intervals, were the same in both studies, Hall *et al.* found that oral misoprostol could induce labour as safely and effectively as vaginal misoprostol, while another study found that vaginal misoprostol was more effective than oral misoprostol. The authors of a fascinating review on the sublingual use of misoprostol in first-trimester surgical abortion found that sublingual misoprostol delivery was an effective alternative to vaginal misoprostol administration for cervical priming.

Although there was a higher incidence of side effects, patient acceptability was very high. According to a review of various trials using the oral and vaginal routes of misoprostol administration, the latest prescribed vaginal misoprostol dose (25 Ag) tends to be more efficacious and safer than the oral doses of 100 Ag. Different methods of misoprostol administration, as correctly pointed out, may not be equal in terms of effectiveness and protection.

Suppositories: In the form of tablets or suppositories, a wide variety of vaginal drugs are available. Some scholars consider vaginal tablets to be a different dosage type and use the words pessaries and suppositories interchangeably. These vaginal formulations are intended to melt in the vaginal cavity and release the drug over a long period of time. Before childbirth and local drug distribution, drugs for cervical ripening are now most widely administered *via* suppository systems. Dehydroepiandrosterone sulphate for uterine cervix ripening, Miconazole for vaginal candidiasis, and progesterone for hormone replacement therapy are all medicines that are offered as a suppository. Binders, disintegrants, and other excipients used in the preparation of traditional oral tablets can be found in vaginal tablets. It has the bonus of being quick to produce and insert. To improve vaginal residence time, mucoadhesive polymers are often used in the formulation of vaginal tablets. Itraconazole, clotrimazole, and prostaglandins are some of the medicines that are offered as vaginal tablets. The presence of hydrophobic and release retarding materials in a vaginal formulation can reduce drug absorption. Drugs that are too hydrophobic for vaginal tablets may not be suitable. Penetration enhancers, such as surfactants and bile salts can greatly increase absorption.

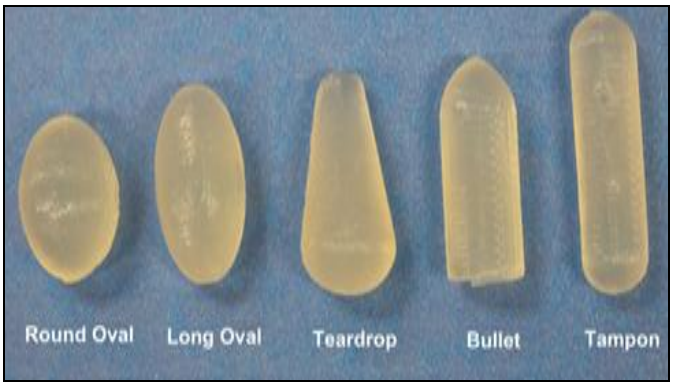

FIG. 5B: SUPPOSITORIES

Bioadhesive Delivery Systems: Modern vaginal formulations have the drawbacks of poor retention to the vaginal epithelium, leakage, and messiness, all of which are unpleasant for the consumer. Bioadhesive, drug delivery systems are being marketed as a solution to these issues. Polycarbophil, hydroxypropyl cellulose, and polyacrylic acid are bioadhesive polymers that have been used in the vaginal formulation. Replens R, a bioadhesive polycarbohil gel, is on the market and is used to preserve moisture and lubricate the vaginal canal. The formulation stays in the vaginal canal for 2-3 days, maintaining the pH of the vaginal canal at a safe, acidic level.

There have also been attempts to administer various peptide and protein drugs using a bioadhesive micro particulate vaginal delivery system. Intravaginal delivery of calcitonin, a polypeptide used in the treatment of postmenopausal osteoporosis, using hyaluronic acid has shown promise for systemic drug administration. There has been a study on a mucoadhesive controlled release drug delivery device for nonoxynol-9, a spermicidal agent. Using the carpool 934P polymer, a gel-type system containing varying levels of nonoxynol-9 and EDTA, a chelating agent, was developed. The car-pool 934P polymer system developed a strong burst release of nonoxynol-9 in the first two min, followed by a six-h duration of controlled release. Gel dosage forms have an advantage over tablet dosage forms in that they have more surface contact and cause less discomfort.

In one research, bioadhesive polymers were used to build a new mucoadhesive vaginal dosage type for the antimycotic drug clotrimazole. Suppositories made of semisynthetic solid triglycerides include polycarbophyl, hydroxypropyl methylcellulose, and hyaluronic sodium salt. These polymers enable the suppositories to remain in the vaginal tract for longer periods of time without causing side effects, increasing the drug's stay on the vaginal epithelium. Mucoadhesive polymers significantly altered the actions of suppositories in terms of adhesive intensity, liquefaction time, and drug permanence in the simulated application site; however, they had no effect on drug release. The formulations developed demonstrated strong technical and adhesion properties and the ability to keep the dosage type at the application site. There have been studies of assemblies for calculating a polymer's bioadhesive strength and retention characteristics in a vaginal delivery system in vitro. In bio adhesion, a modified simulated vaginal fluid was used. A model membrane was developed using isolated lamb vaginal epithelium and cellophane saturated with simulated vaginal fluid. The measurement of tensile strength or shear stress needed to break the adhesive bond between a model membrane and a test formulation is the basis for bio adhesion. The delivery system is mounted between two model membranes fixed on flexible supports in the assemblies for a set period of time.

The force required to separate the adhesive bond is measured and calculated as bioadhesive strength after the bond is formed. These assemblies can be used to compare the bio adhesion and retention properties of different polymers *in-vitro*. Bioadhesive Tablets are being tested. The Monsanto hardness tester was used to measure the hardness of each batch's formulated tablets (10 in total) (Tab Machines, India). The procedure defined in USP was used to assess friability. The mass variation of the formulated tablets (20 in total) was checked according to Indian Pharmacopoeia procedures. A 1% agar gel plate at 370 °C was used to monitor the swelling rate of bioadhesive tablets.

The bio adhesive strength of porcine vaginal mucosa was calculated using acetate buffer, pH 6.0, as a model membrane and acetate buffer, pH 6.0, as a moistening fluid. The mucosal membrane's surface was blotted with filter paper before being moistened with acetate buffer. Bioadhesive strength was determined by force needed to remove the tablet from the mucosal surface. The thickness of the vaginal mucosal membrane was 0.01-0.05 mm and the temperature was maintained at 37 °C throughout the study. Porcine vaginal mucosa was collected from three separate animals for each experiment. Within 1 h of sacrificing female pigs at the local slaughterhouse, vaginal mucosa was collected. Female pigs were 1.5 0.5 years old (on average SD). Level of dissolution, the USP style 5-paddle system was used to perform the *in-vitro* dissolution experiments. A 65:35 ratio of 0.1 mmol L-1 pH acetate buffer 6.0 and dioxane were used in the dissolution medium.

The temperature of the medium was kept at 371 °C, and it was stirred at 100 rpm. At acceptable time intervals, samples (3 ml) were removed and compensated with a fresh dissolution medium before being spectro-photometrically calibrated at 270 nm. None of the ingredients in the matrix formulation were found to interfere with the assay. Each experiment was carried out three times [45].

Approaches of Novel Drug Delivery Systems for Anti-HIV Agents:

Nanoparticles: Nanoparticles may be solid colloidal particles or suspended in liquid media, with particle sizes varying from 1 to 100 nano-meters. The size of these particles can be varied and effectively launched for site-specific and sustained drug release, depending on the polymer type and ratio in the formulation designed. This principle is more effective with molecules that have weak physicochemical strategies, such as insolubility and instability.

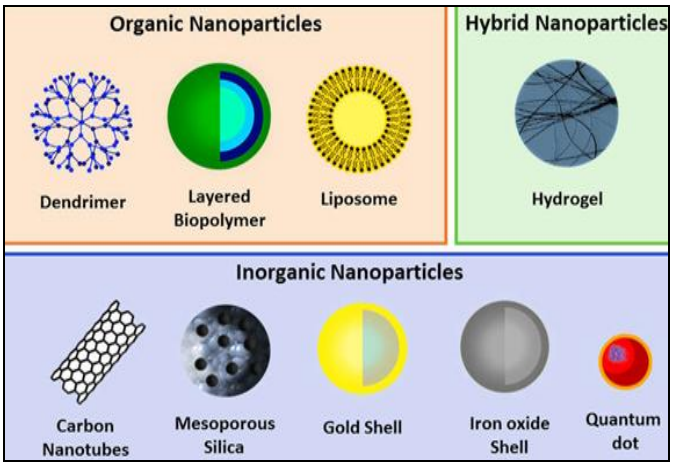

FIG. 6: NANOPARTICLES

The uptake of these nanoparticles was superior to that of the pure drug when treated with macrophages isolated from HIV-positive people. Similarly, when Saquinavir and DDC nanoparticles were formulated with poly (hexacyanoacrylate) using an emulsion polymerization technique, the nanoparticles had a significantly higher efficiency than the pure drug suspension. Loberberg, Ananjo, and Kruter performed an *in-vivo* analysis in rats to investigate the oral delivery of AZT attached to hexacyanoacrylate nanoparticles for reticuloendothe lial cell delivery. The uptake of AZT nanoparticles by pronuclear leukocytes was demonstrated in a recent in-vitro study, in which the effect of nanoparticles prepared with poly (lactic acid) poly (ethylene glycol) polymer was found to be PEG ratio-dependent. The nano systems, on the other hand, gain easy access to the brain through the process of endocytosis, which can also move away from the efflux pump's location.

Nanopowder: For the enhancement of solubility and drug release rate of many hydrophobic drugs, nanopowders have been successfully used through the peroral route of drug delivery. When the morphology of Loviridine nanopowder was studied, plate-like features were discovered, while the untreated material showed crystal structures.

Nano-containers: The principle of ARV targeting using carriers such as dendrimers has also been extensively investigated. Dendrimers are macro-molecules with spherical and strongly branched structures that are synthesized. Because of their structural uniqueness, these macro-molecules have emerged as a sought-after tool by existing drug carriers for targeted delivery. As a result, they were initially established for the purpose of targeting antiretroviral drugs.

Nanocontainers based on poly (propylene imine) dendrimers target Efavirenz (EFV) to Mo/Mac. Since they behave like a closed nanosize vessel with an entrapped drug inside, these molecules are referred to as nanocontainers. Furthermore, mannosylated PPi dendrimers have been reported as a promising carrier mechanism for antiretroviral drug delivery, such as EFV.

Liposomes and Ethosomes: Liposomes are vesicular structures made up of phospholipids and cholesterol that are used to deliver medicines that are both water and oil-soluble. The same approach was used to deliver Azidothymidine (AZT), which was studied using a mouse model. When AZT encapsulated in liposomes is compared to the free drug, the results show that there is no bone marrow toxicity. In monocytes, macrophages, and HIV-1 infected macrophages, didinasin encapsulated for improved half-life achieved a half-life of 24 h from 3, 4 h, and the liposomes displayed greater cell uptake and anti-hive activity than free didinasin.

The ethosomes, a type of vesicular system with a high composition of phospholipids and alcohols, have been found to have a better effect than liposomes in the delivery of anti-HIV drugs.

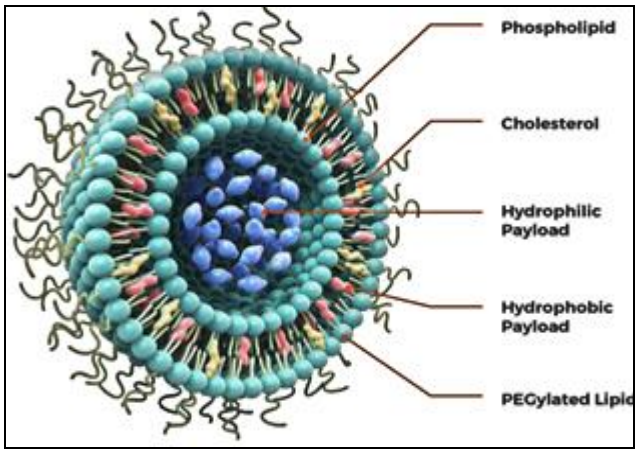

FIG. 7: LIPOSOMES

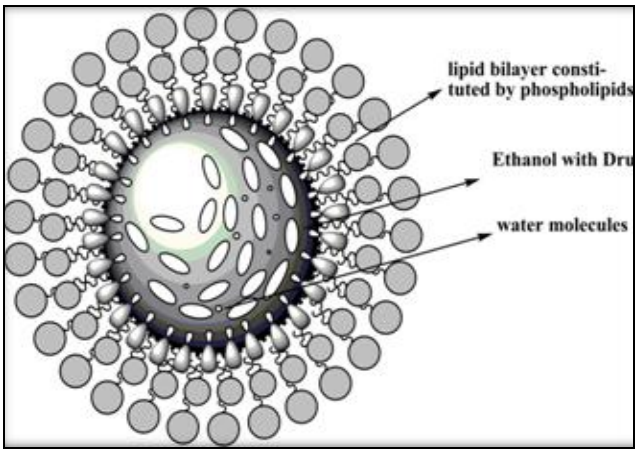

FIG. 8: ETHOSOMES

Transdermal: Because of the major advantages of a non-parenteral route for drug delivery, avoidance of first-pass metabolism (gut and hepatic as well), GI degradation, reduced side effects by minimizing plasma fluctuation, and excellent targeting of the drug for better patient compliance, the transdermal method has gained momentum. The most difficult problem and limitation of the transdermal route of absorption is the unpredictable and low cutaneous transport for molecule uptake. The majority of studies centered on improving drug penetration by salt formation, solvent and co-solvent addition, iontophoresis, or anodal current application. Litho simple or combination helps increase ARV drug permeation. In addition to polymeric ingredients, including gum matrix, transdermal gels and patches have been developed for AZT. Various *in-vivo* and *ex-vivo* experiments on ARV drugs such as ddI, ddC, and AZT using animal skin such as rat, mouse, pig, and human cadaver have shown the efficacy of these ARV drugs when administered transdermally [46].

Recent Advances in Vaginal Drug Delivery System: As pharmaceutical technology progresses, modern delivery methods such as suppositories, capsules, creams, and gels are displacing traditional delivery systems. Women's views on vaginal products must be taken into account in the production of appropriate dosage forms and strengthened enforcement. Among the numerous new delivery systems, mucoadhesive systems hold a special place. Mucoadhesive polymers have been used to deliver systemic and local vaginal drugs with great success. For the preparation of mucoadhesive vaginal drug delivery systems, acrylic acid polymers (Carbomer or polycarbophil) and cellulose derivatives such as hydroxy-ethylcellulose, hydroxypropylcellulose, and hydroxypropyl methylcellulose have been commonly used as mucoadhesive polymers. Both types of polymers are of the subject a variety of patents. Polyacryclic acid polymers, in particular, are excellent multipurpose vehicles for vaginal drug delivery. Vaginal lubrication, contraception, vaginal diseases, labour inducmnte and infertility are also handled with existing programmes. Gels have a range of benefits over other types of pharmaceutical drugs, including patient compliance with administration and ease of delivery of the pharmaceutical product on the vaginal mucosa's surface. Gels, in particular, have the added benefit of hydrating and lubricating action, which is especially useful in pathological conditions marked by dryness of the vaginal mucosa due to the high water content in their structure.

Despite the various proprietary vaginal gel formulas, there are only a few commercially available gel preparations. The bulk of them are used for vaginal moisturization and contraception. There are no commercially available mucoadhesive vaginal tablet formulations that we are aware of. When looking at current patents for mucoadhesive vaginal drug delivery systems, it's easy to see that there are a lot of them. Furthermore, since this is a general complaint, these patents say a number of items. For example, some of them have a large number of active and inactive ingredients in a wide variety of amounts, or one parent claims to have several dosage forms in the same application, such as gel, ointment, pill, film, or suppository. This argument was specifically written to extend the scope of patents in order to make patent

infringement impossible. Finding precise patents and claims is exceedingly difficult. Many of the arguments were found to be greatly exaggerated. As a consequence, it's difficult to concentrate on a particular target. It may be natural for applicants to extend the reach of their patents, but this makes new applications difficult, if not impossible. Despite the fact that there are only a few commercially available mucoadhesive vaginal drug delivery systems, mucoadhesive vaginal drug delivery systems will become more relevant in the near future as the number of sexually transmitted diseases such as HIV increases [47].

- Applications 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 [48].

CONCLUSION: The vaginal route has been rediscovered as a possible route for systemic delivery of a variety of therapeutically effective drugs that prevent the first-pass metabolism. However, due to poor absorption of certain medications through the vaginal epithelium, successful drug delivery via the vaginal remains a challenge. The rate of drug absorption after vaginal administration is influenced by a number of factors such as vaginal physiology, patient age, and menstrual cycle. Bioadhesive tablets, liposomes, niosomes, and microparticles, which are still relatively new but show great promise in providing truly managed drug delivery, are the future of vaginal drug delivery. At present, vaginal drug delivery systems include vaginal rings, pessaries, suppositories, bioadhesive capsules, and some bioadhesive microparticulate systems. The use of nanoparticles in vaginal drug delivery systems is a growing trend in science. Other than contraceptives and vaginal infections, recent research has looked at using these delivery mechanisms to treat cancer and distribute different protein and peptide drugs. Vaginal delivery systems have the potential to be used even more commonly than they are now. To fulfill these opportunities, it is hoped that novel bioadhesive systems, both microparticulate and nonparticulate, will be produced promptly. Antiretroviral drug therapy conflicts have been settled by adapting different experimental drug delivery approaches, which has provided a medium for many scientists to demonstrate the effectiveness of their techniques. Even though some promising developments are emerging in this area, vesicular systems such as liposomes and nanosized systems such as nanoparticles receive more publicity and significance than the other schemes. Because of the complexity of viral infections, multi-disciplinary research is needed for formulation design and optimization of analytical techniques before these NDDS products can be commercialized. This is particularly true for ARV drugs. Certainly, emerging methods, such as new medicinal agents and regimens, will make a huge difference in the lives of HIV-positive people in the future.

ACKNOWLEDGEMENT: None to report

CONFLICTS OF INTEREST: There is no conflict of interest.

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How to cite this article:
Mehetre NM and Singh I: Therapeutic carriers for the vaginal delivery of anti-hiv drug. Int J Pharm Sci & Res 2022; 16(2): 543-58. doi: 10.13040/IJPSR.0975-8232.13(2).543-58.