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REVIEW ARTICLE

AN EXHAUSTIVE STATISTIC ON CURRENT MUCOADHESIVE INTRAVAGINAL DRUG DELIVERY METHODOLOGIES

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ABSTRACT
The vaginal course of medication conveyance offers many focal points because of its huge permeation range, rich vascularization, avoidance of first pass metabolism and relatively low enzymatic activity. A few examinations have demonstrated that for sedate organization the vaginal pit is a viable course which expected for the most part for neighborhood activity and conveying drugs for foundational impacts with uterine focusing on. It was first Sobrero who endeavored the vaginal mucosa for tranquilize assimilation, from that point forward much research has been done on the organization of medications through this course. As of late, for vaginal dose frame, different plan and application has expanded impressively. It is fundamentally the conveyance of medications inside or through the vaginal mucosa for neighborhood or foundational pharmacological activity. Degree of medication ingestion and its rate after organization may shift contingent upon vaginal physiology, age of the patient, arrange in the menstrual cycle, neurotic conditions and detailing factors. Here in this audit, there's a feature, the advantages and confinements of vaginal medication conveyance, philosophy in assessment of vaginal medication conveyance frameworks, pharmaceutical viewpoints and an outline of late advances made in the bailiwick of vaginal medication conveyance. Advancement of measurements frame in various stages and in the market, are likewise audited.
Keywords: Intra-vaginal drug delivery, vaginal delivery, microbicide delivery, solubility modifier, first pass metabolism.

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INTRODUCTION

Novel researchers have shown their interest on mucoadhesive drug delivery systems among them; vaginal drug delivery system offers a thoroughfare for the release of different antifungal, antibacterial and contraceptive drugs. To improve the vaginal therapy, the formulation administered via the vagina should have more residence time in the vaginal cavity. Conventional vaginal dosages forms have pros and cons both, like they avoid the first pass metabolism, easy to formulate, self-administration, and are economical whereas it produces itching, irritation of vagina, messy to apply, and low residence time respectively. Therefore, to overcome nano drug delivery systems are being formulated. Recently nano drug delivery systems like vaginal liposomes, vaginal niosomes, nano suspensions, nano emulsions, nanofibres, have evoked more interest to deliver the drugs via the vaginal route. They offer increased residence time, cellular targeting, localization of formulation to specific sites and mucoadhesion. Various mucoadhesive polymers like hydroxylpropyl methylcellulose (HPMC), chitosan, sodium alginate, eudragit, polycarbophil, carrageenan, hydroxypropyl cellulose, ethylene (vinyl acetate) co- polymer among others have been used for developing novel vaginal formulations. For prevention of HIV and other sexually transmitted diseases (STDs)[1] topical delivery of microbicides is also being investigated as an alternative option.

Merits of bioadhesive systems over the existing conventional preparations:

- Excellent accessibility[2]
- Avoidance of aqueous or organic solvents,
- Easy of self-administration[3]
- Gel like consistency in the activated state or at the body temperature[4]
- No irritation

- Rapid bioadhesion, prolonged residence time in the vaginal cavity even in absence of physiological secretions[5].
- Extended dosing interval[6].
- Improved chemical and physical stability[7].

Mucoadhesive vaginal delivery systems have both synthetic and natural polymers. Most commonly used mucoadhesive polymers that are capable of forming hydrogels are synthetic polycarbophil, chitosan, cellulose derivatives (hydroxyethycellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose), pectin, hyaluronic acid derivatives, polyacrylates, tragacanth, carrageenan and sodium alginate. New mucoadhesive molecules are thyolated polymers. There bioadhesive properties are cinched by polyacrylic acid-based polymers, known as Carbomers. Mercantilelycarbomers are available in different grade, molecular weight, residual component or degree of cross-linked structure. Among these polymers, polycarbophil and polyacrylic acid are cross-linked with divinylglycol and are more preferred also. These water insoluble polymers have an apparent pKa of approx 4 and picks up 61-100 times its weight in water[8-10].

Disadvantages

- Gender specificity,
- Patient incompliance,
- Only a few drugs are administered by this route[11].
- Variability in drug absorption related with menstrual cycle, menopause and pregnancy,
- Influence with sexual intercourse[12].
- Personal hygiene.
- Some drugs are sensitive at vaginal pH[13].

ANATOMY AND PHYSIOLOGY OF VAGINA

The human vagina is a fibro muscular tube which is capable of collapsing. It is a passageway that connects the cervix, which is the opening of the uterus, to the outside of the body. It is also known as the birth canal. The length of the vagina is 6-10 cm which widens from the cervix[14]. The wall of human vagina comprises of three layers such as:

- An outer adventia layer.
- Middle muscular layer.
- The tunica adventia.

It has contours called rugae at the walls of vagina in close juxtaposition to each other which form a collapsible tube. The epithelium portion does not contain any glands, but its surface is kept moist due to cervical secretion, whose composition and volume varies with age, stage of menstrual cycle and degree of sexual excitement. Drug absorbed via the vaginal route which avoids first pass metabolism because the blood leaving from human vagina directly enter into peripheral system through different veins. The normal human vagina lumen has an acidity of around pH 4-5. This vaginal pH is due to the active secretion of ovarian hormones and is also invariantly maintained by the sloughing of mature cells in the upper layers of vaginal mucosa. Due to the influence of estrogen, these cells contain a content of glycogen, which is metabolized to lactic acid in the vaginal canal which maintain the vaginal pH on the acidic side, whereas, the acyclic luteal influence on the vaginal mucosa significantly increases the pH value.

VAGINAL ANATOMY AND PHYSIOLOGY WITH RESPECT TO DRUG DELIVERY

The vaginal secretion, pH, enzyme activity and microflora makes the vagina remarkably linguistics. These factors affect formulation spreading, retention, absorption and drug release in vagina.

Vaginal Secretions: The release is a blend of numerous emissions that is gathered in the vagina from peritoneal, follicular tubal, uterine, Bartholin's and Skene's organs.[15] Here in nearness of dampness, strong dose plans ought to be in a perfect world scattering in the vaginal trench instantly after inclusion to maintain a strategic distance from bother to the clients.

Catalyst Activity: The particular enzymatic action diminishes arranged by four diverse amino peptidases in vaginal homogenates i.e.: sheep > guinea pig > rabbit ≥ human ≥ rodent.[16] The human genital tract has bring down enzymatic action which prompts less debasement of protein and peptide sedates in the vagina than the gastrointestinal tract.

Vaginal pH: The pH of the healthy female genital tract is acidic (pH 3.5–4.5) and is maintained within that range by conversion of glycogen from exfoliated epithelial cells to lactic acid through bacteria[17]. Changes in the pH are with age, stage in the menstrual cycle, infections, estrogen levels and variations in the levels of cervical mucus. A successful vaginal drug delivery is a critical factor for controlling the vaginal ph[18].

The change in hormone levels with age, during intercourse and various phases of the menstrual cycle leads to alteration in vaginal secretion, pH, enzyme activity as well as changes in the thickness and permeability of the epithelium all of which complicate the problem of achieving consistent drug delivery[19].

MECHANISM

The mechanism of mucoadhesion is generally based into two steps;

- Contact stage
- Consolidation stage.

The first stage is an intimate contact, formed between the mucoadhesive and mucous membrane. Initially its contact with the mucus layer is deep. While in the consolidation stage, presence of moisture activates the mucoadhesive material. System is plasticized by moisture and allowing the mucoadhesive molecules to break free and attached by weak Vander Waals and hydrogen bonds. The diffusion theory and the dehydration theory are the two theories that explain the consolidation step. Mucoadhesive molecules and the glycoproteins of the mucus mutually interact and interpenetration their chains and the building of secondary bonds. This is performed according to diffusion theory. For this to take place, the mucoadhesive device favored both chemical and mechanical interactions. For example, molecules having hydrogen bonding groups (-OH, -COOH), high

molecular weight, an anionic surface charge, flexible chains and surface-active properties, which helps in spreading throughout the mucus layer[20-29].

Theories Mucoadhesive is a complex process having numerous theories; their mechanisms are explained as below:

Wetting Theory: The wetting theory is the oldest theory of adhesion. Applied on low-viscosity bio adhesive or liquid systems which present affinity to spread over the surface. Predominantly applicable to liquid bioadhesive systems. The thermodynamic work of adhesion is a function of surface tension of the surface in contact as well as interfacial tension. The interfacial energy is responsible for the contact between the two surfaces and adhesive strength. By using measuring techniques such as the contact angel, liquids are spread over the surface and leads to the greater affinity. There is no contact angle to provide good spread ability. The spread ability coefficient (SAB) can be calculated by the difference between the surface energies γB and γA and the interfacial energy γAB. Hence this theory tells about the importance of contact angle and reduces the surface and interfacial energies to gain good amount of mucoadhesion.

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Dispersion Hypothesis: Here the polymer chains and bodily fluid blend to an adequate profundity to make a semipermant cement security. Attachment compels increments with the level of infiltration of the polymer chains and dissemination coefficient have property to improve/diminish the entrance rate of dispersion, adaptability. Nature of the mucoadhesive chains, versatility and contact time likewise rely upon dispersion coefficient. Profundity of interpenetration required to create a productive bioadhesive security lies in the range 0.2-0.5. Given condition is utilized to identify the interpenetration profundity of polymer and mucin chain.

$$l = (tD_b)$$

Where t is the contact time and D expressed asthe diffusion coefficient of the mucoadhesion material in the mucus. To achieve the adhesion strength of polymer, the depth of penetration is approximately equivalent to the chain size of polymers. If components have good mutual solubility then proper diffusion should be occurred. Bio adhesive and the mucus have similar chemical structures. If structural similarity is more than mucoadhesive bond is better.

Fracture Theory: The most used theory in studies on the mechanical measurement of mucoadhesion is fractional theory. It attempts to relate the difficulty of separation of two surfaces after adhesion which is used to analyze the force required to separate two surfaces after adhesion is established. This force Sm is calculated in tests of resistance by the ratio of maximal detachment force Fm and the total surface area A0 involved in the adhesive interaction.

$$S_m = F_m/A_0$$

Since the fracture theory is used only for the force required to detach the parts and not used to measure interpenetration or diffusion of polymer chains. It is used to calculate solid or semi-solid bio adhesive materials, in which no penetration of the polymer chain into the mucus layer.

Electronic Theory: Hypothesis is used to describe that when when electron exchange between the bodily fluid and the mucoadhesive framework, bond ought to be happened, and through contrasts in their electronic structures is emerge. When electron is transfer between the mucus and the mucoadhesive, double layer of electrical charges at the mucus and mucoadhesive interface is formed. The net result of this process is the formation of attractive forces within the double layer.

Adsorption Theory: After an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. In this theory, adhesion is the result of various surface interactions (primary and secondary bonding) between the polymer that is adhesive on surface and mucus substrate. Chemisorption required forming primary bonds and ionic, covalent and metallic bonding play an important role in adhesion, which is generally undesirable due to their permanency. Vander walls forces, hydrophobic interactions and hydrogen bonding are responsible for formation of secondary bonds. To break these interactions less energy is required, they are the most well-known from of surface interaction in mucoadhesion process due to having semi-permanent bonds. All these theories are involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. These theories are considered as supplementary process. Each and every theory is equally describing the mucoadhesion process. Mucin is initially wetting and then diffusion of the polymer into mucin layer and formation of fractions in the layers, the adhesion or electronic transfer or simple adsorption phenomenon should be affected that finally leads to the perfect mucoadhesion. Formation of mucoadhesive bond is depending on the nature of the mucus membrane, mucoadhesive material, the attachment process and the subsequent environment of the bond.

VAGINAL ROUTES OF DRUG ABSORPTION

The drug is delivered in the vagina mainly via two routes: intravaginally to the vaginal epithelium or transvaginal through the vaginal mucosa to uterus and systemic circulation. Cicinelli *et al*. reported that the vagina has specific blood flow characteristics, either by a portal type circulation or by venous and lymphatic channels that allow bypassing the gastrointestinal tract absorption and liver detoxification and permit preferential transport of drug molecules from the vagina to the uterus and systemic circulation.[30] Several physical models have been devised to study the vaginal permeability of drugs[31]. Antifungal agents such as tioconazole, clotrimazole and miconazole are topically administered to treat vaginal yeast infections. On the basis of our knowledge of anatomical and physiological features of the vagina, it is likely that many other drugs will be formulated for vaginal administration in the future[32-39].

The vagina as a site for microbicide delivery

Significant advance has been accounted for in the zone of vaginal microbicides. There are currently more than

50 potentially microbicidal products under development globally, of which 16 are in Phases I-III clinical trials. Recently, the vagina has been rediscovered as potential route for microbicide and contraceptive delivery. Acid form is a gel definition that keeps up a low vaginal pH, immobilizes sperm and forestalls duplication and survival of STD causing creatures[40-41]. Cellulose acetate phthalate based sponges and those made from other cellulose derivatives are soft, mechanically resilient and thus ideally suitable as bio-erodible microbicidal vaginal devices[42]. Conceival is a novel non-toxic, nonspermicidal, self emulsifying lipophilic gel with improved solubility of lipophilic anti-HIV microbicides[43]. Another vaginal product under development is a liposome preparation containing monoclonal antibodies that will completely agglutinate sperm in the ejaculate.

Pharmaceutical aspects

Many pharmaceutical organizations right now concentrate on the advancement of novel vaginal medication conveyance frameworks for treatment of vaginal contaminations, sexually transmitted diseases, contraception and other gynecological conditions. These innovative delivery systems may lead to extended product shelf life making the products competitive in the market place. The option approach of definitions based pharmaceutical organizations is grow new measurements frames utilizing novel excipients that offer particular preferences over ordinary medication conveyance frameworks. With a specific end goal to accomplish alluring medication attributes diverse methodologies are utilized[44]. The compatibility between the drug and excipients can easily be evaluated by thermal (Differential Scanning Calorimetry) and isothermal (HPLC) stress testing.[45]

Penetration Enhancers: Penetration enhancers are capable of promoting absorption and penetration of drug through the vaginal mucosa by decreasing the penetration barrier[9,46]. Currently, the most preferred penetration enhancers include non-ionic surface-active agents, bile salts, benzalkonium chloride, hyaluronic acid[47], polyethylene glycol, ethoxydiglycol and inter esterified stone oil[5, 20].

Solubility Modifiers: The poor solubility of drugs in simulated vaginal fluid may affect the release pattern of a drug from its device, which influences the onset and therapeutic efficacy of the drug. Water-soluble drugs are good candidates for vaginal drug delivery. The aqueous solubility of a drug can be increased by several mechanisms such as addition of solubilizing agents and cosolvency[48]. The most commonly used solubilizing agents include citric acid, ethylenediaminetetraacetate, sodium meta-phosphate, polyvinyl pyrrolidone, sorbitan, tween 80, polyoxyethylene, polyoxyethylene n-alkyl ethers, poloxamers, and cyclodextrin[49]. For example, a novel itraconazole formulation intended for vaginal use is based on hydroxypropyl-β-cyclodextrin, a functional excipient that increases drug solubility[50].

Mucoadhesive agents: Mucoadhesive agents permit a close contact of formulation with the vaginal mucosal surface by promoting adherence[51]. These include polycarbophil, hyaluronic acid, chitosan, sodium alginate, tragacanth, carbomer, acacia, sodium carboxymethyl cellulose or other cellulose derivatives, Carbopol 974P-NF, Carbopol 971P-NF and other copolymers of acrylic acid[52]. Some of these polymers may possess sitespecific bioadhesive properties. For example, xanthan gum and sodium alginate show sitespecific bioadhesive properties in a simulated vaginal environment[53]. Polycarbophil 934P exhibited pH-dependent bioadhesive properties[54].

CONVENTIONAL VAGINAL DOSAGE FORMULATIONS

Vaginal tablet: Vaginal tablets are prepared in such a way that they will melt, or disintegrate in the vagina and release the medication in the cavity. Vaginal tablet contains all the excipients of a normal conventional tablet. The tablets are prepared by direct compression method and effervescing agents can be incorporated into formulations to enhance the swellabilty and release of the drug[54]. Tablets offer the advantage of ease of manufacture and insertion. Tablets are stable and less messy to handle than creams or ointments. For example, Clotrimazole vaginal tablet have been used to prevent vaginal candidiasis. Ultra-low dose estriol and Lactobacillus acidophilus vaginal tablets (Gynoflor®) were found to be effective in treating vaginal atrophy in postmenopausal breast cancer patients[55-58]. Bio adhesive vaginal tablets containing cyclodextrin complex of itraconazole were developed to prevent vaginal candidiasis. Vaginal creams are used to deliver the antifungal, antibacterial and contraceptive drugs topically[59-62]. Vaginal creams are messy to apply, uncomfortable and sometimes embarrassing when they leak into the underclothing. Also, the exact dose is not provided because of the heterogeneous distribution of the formulation when applied into the vagina as they are easy to use, formulate and are easily available. Premarin vaginal cream is indicated for the treatment of patients with refractory endometria[63]. Conjugated equine estrogen vaginal cream can be used to relieve menopausal atrophic Vaginitis. Bacterial vaginosis can be treated by clindamycin cream. Dienoestrol cream may be useful in the symptomatic prevention of vaginal atrophy in postmenopausal women. Postmenopousal vaginal atrophy can be treated with ovestin vaginal cream and estradiol vaginal cream[64].

Vaginal foam: Vaginal foams are contraceptive foams, used to prevent conception. Spermicide is added in vaginal foam to destroy the sperm and reduce the chances of pregnancy. The foam produces a partition between the sperm and the egg. It is very essential to administer the foam correctly and intercourse should be happening within 1h. Advantages of vaginal foams include availability in market and can be used as a lubricant during sexual intercourse. Different disadvantages have been reported like they produce messiness, not effective against other sexually contagious diseases, may produce inflammation, irritation of vagina, and should be used with other contraceptive device to make it effective. Vaginal froth containing a remedially compelling measure of rifaximin was observed to be helpful in the treatment of vaginal diseases, especially bacterial vaginosis.[64]

Vaginal gel: Vaginal gels containing antibacterial drugs have been used to prevent various vaginal infections. They can also be used to reduce vaginal irritation, discharge and other sexual problems. Bacterial vaginosis is an infection of the vagina caused by overgrowth of the bacteria and this infection can be treated by vaginal gel[65-71]. Vaginal gels have been commonly used to deliver agents that tighten the vaginal area by contracting the vaginal muscles, helping in enhanced sexual pleasure. In vaginal dryness, gels are used as a lubricant. Some disadvantages of vaginal gels are that they are contraindicated during menstruation and pregnancy. They may suffer from leakiness and messiness. Examples: Hyaluronic acid vaginal gel can be applied in case of vaginal dryness. Researchers have found that certain vaginal gel having antiretroviral drugs may decrease the risk of HIV infection among women. Tenofovir vaginal gel has been investigated in the prophylaxis of HIV vaginal suppositories. There are a large number of vaginal suppositories in the market which are used to release antifungal and antibacterial drugs in the vagina for different vaginal infections. Reported advantages with vaginal suppositories include avoiding the first pass metabolism, ease to formulate, and self- administration. Different disadvantages are also seen like they produce messiness, less bioadhesion, contraindicated during pregnancy and other sexual problems. For example, vaginal suppositories with lactobacillus were formulated and evaluated to decrease the recurrence of urinary tract infections (UTI) following antimicrobial therapy. Progesterone vaginal suppositories were developed for the prevention of premenstrual syndrome. Prostaglandin suppositories were found to be effective for vaginal infection. Amphotericin B vaginal suppositories were developed for the treatment of non-Candida *albicans vaginitis* in women. Prostaglandin E2 vaginal suppositories were found to be efficacious in the treatment of persistent postpartum uterine atony.

NOVEL VAGINAL DOSAGE FORMULATIONS

Controlled/sustained release vaginal tablets

Conventional vaginal tablets release the drug immediately and do not offer prolonged or controlled release of the drugs. Many chronic illnesses and recurrent infections may require prolonged therapy. Therefore controlled/sustained release vaginal tablets have been developed. These tablets may employ various rate sustaining polymers such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose, sodium alginate, ethyl cellulose, guar gum, xanthan gum, etc. Also, the mucoadhesion of the tablets can be improved by using mucoadhesive agents such as chitosan, polycarbophil, etc. Tenofovir vaginal tablet was investigated to deliver tenofovir as a potential HIV microbicide.[72]

Vaginal ring

Vaginal ring is fabricated by dispersing a contraceptive steroid, such as medroxy progesterone acetate, as micronized solid particles in a viscous mixture of silicone elastomer and catalyst and then extruding the steroid polymer dispersion into a mould to form a vaginal ring[73-76]. They are designed to be inserted into the vagina and position around the cervix for 21 days to achieve a constant plasma progestin level and cyclic intravaginal contraception. Reported problem associated with the use of vaginal rings are erosion of vaginal wall, ring expulsion, interference with coitus, unpleasant ring odour, difficulty with storage and sanitation, premature discontinuation due to vaginal discomfort and device related events, including foreign body sensation. For example, Asilastic vaginal ring impregnated with medroxyprogesterone acetate was used as contraceptive device. A novel contraceptive vaginal ring releasing etonogestrel and ethinylestradiol was used to control the menstrual cycle and the bleeding[78]. Oestradiol releasing vaginal ring has been investigated for the treatment of postmenopausal urogenital atrophy. Novel vaginal danazol ring therapy for pelvic endometriosis has been investigated. Vaginal microspheres are designed as innovative vaginal drug delivery system to impart stability to drug molecules, improve bioavailability and to produce controlled as well as targeted drug release. Bioadhesive micro particles and mucoadhesive microspheres are used for better prevention of different diseases[79]. Vaginal microspheres have several advantages such as constant and prolonged therapeutic effect, mucoadhesion, reduction in dose frequency and better patient compliance. But disadvantages also have been reported like higher drug loading required, batch to batch non-uniformity, variation in release rates and toxicity[80]. Econazole nitrate polymer– lipid based vaginal mucoadhesive microspheres were prepared by using spray congealing method. Hyaluronan ester vaginal microspheres were designed for the release of salmon calcitonin to treat the vaginal infection.

Vaginal nanoparticles

Because of less duration of action and incomplete coverage, the effect of administered drugs via vaginal route reduces. Therefore, to obtain prolonged release, cellular targeting, and for the treatment of several vaginal infectious disorders, vaginal nano particles have been formulated. These nano particles may contain several mucoadhesive polymers such as chitosan, polycarbophil to improve the mucoadhesion so as to achieve better therapeutic efficacy. Example: mucus penetrating nano particles for vaginal drug delivery were used to protect against herpes simplex virus.[81] Vaginal liposomes consisting small interfering RNA were designed to inhibit different vaginal infectious diseases.[82]

RECENT DEVELOPMENTS IN VAGINAL DRUG DELIVERY SYSTEM

Vaginal films containing Abacavir, a potent nucleoside reverse transcriptase inhibitor, were designed for the inhibition of sexually transferred diseases[83]. The films were formulated by solvent evaporation method. The resulted films produce extended release of the drugs and they can be applied as novel drug delivery system for the treatment of sexually contagious diseases. Chitosan embedded liposomes incorporating clotrimazole were designed and the results showed it as a promising formulation for vaginal topical therapy.

EFdA (a proprietary topical microbicide) films were formulated to treat different sexually transmitted diseases. Fast dissolving films were made with PVA, HPMC E5 and propylene glycol and the produced films were applied intravaginally[84]. The results indicated that they can be used for the effective prevention of HIV infection. Olive oil based emulsion hydrogels have been produced for the treatment of sexually contagious disorders. In this case, sorbitan mono palmitate was added as a structuring agent. The resultant films were biocompatible and showed non-Newtonian flow and can be used to prevent sexually transmitted infections[85]. Curcumin liposomes were prepared for the inhibition of vaginal infections. In this case mucoadhesive polymers like chitosan and Carbopol have been used to prepare the liposomes. Then different physiological properties including mucoadhesion strength were checked and it was revealed that the formulated mucoadhesive liposomes were useful as novel delivery system for vaginal infections[86]. Mucoadhesive caplets of 3′-azido-3′-deoxythimidine and polystyrene sulfonate (anti-HIV drug) were developed and characterized. Different mucoadhesive polymers like ethyl cellulose, polyacrylic acid have been used to prepare the caplet. The results proved that mucoadhesive caplets of the above drug can be used as potential drug delivery systems for treatment of HIV infected patients.

Bio adhesive mini tablets were formulated and evaluated for the vaginal delivery of hexyl amino levulinate hydrochloride[87]. Different nonionic cellulose ethers and MCC were investigated as matrix forming agents. The resultant mini tablets increased the residence time in the vaginal mucosa and therefore sustained release of the drug can be obtained. Novel silicone elastomer vaginal gels of maraviroc were developed and evaluated. The resultant gels were found to release the drug in a sustained manner. In a study, Cross linked Polyethylene glycol (PEG) based hydrogels of the antimicrobial subtilosin were developed and studied[88]. Characterization study proved that these hydrogels offered extended release of subtilosin for the prevention of bacterial vaginosis. Ethylene-vinyl acetate (EVA) copolymer vaginal rings containing progesterone were developed and evaluated. The rings having silicone were prepared by hot melt extrution method to release progesterone via the vagina. Solid lipid nanoparticles embodying antifungal drugs like ketoconazole, clotrimazole were prepared and evaluated. In this case PEG 40 stearate has been used and it reacted with acryloyl chloride to form a polymerisable moiety which produced a second shell for slow release of drugs[89]. Then *in vitro* studies of drug permeability revealed that the nano particles can be used for the inhibition of vaginal infections. UAMC01398, a diaryltriazinenon-nucleoside reverse transcriptase inhibitor was formulated as a gel and evaluated for anti-HIV microbicide activity. To produce the best formulation, different hydroxyethyl cellulose based gels were investigated to check their toxicity, stability, ability to enable UAMC01398 epithelial permeation[90]. The result indicated that UAMC01398 has the potential to act as anti-HIV microbicide. Curcumin hydroxyl propyl cyclodextrin vaginal films have been formulated to treat cervical cancer caused by Human Papilloma Virus (HPV). In this case, solvent evaporation process was used to form the films by using HPMC E15 and carbopol 934P. It was concluded that these films offered longer residence time in vagina and have the potential to treat HPV induced cervical cancer[91]. Double reservoir polyurethane intravaginal rings were prepared to treat sexually transmitted diseases and uncontrolled pregnancy. Dual reservoir vaginal rings were designed in such a way that they will release tenofovir (HIV- 1 reverse transcriptase inhibitor) and levonorgestrel (contraceptive) for a prolonged period. Oxybutynin vaginal rings for alleviation of overactive bladder symptoms in women have been developed. From the in *vivo* test it was revealed that these rings were well tolerated and have the potential to act as a novel drug delivery system for the prevention of overactive bladder symptoms.

Lyophilized liposomal gels containing antiviral drug, acyclovir, for the intravaginal delivery were formulated and evaluated. Liposomes were prepared by rotary evaporation method with carbopol and HPMC and subsequently lyophilized. From the evaluation, it was revealed that the carbopol gels showed higher viscosity, spreadability and mucoadhesiveness than the HPMC gels, therefore carbopol liposomal gels were proposed as a promising delivery system of acyclovir via the vaginal route[92]. Fluconazole nanofibres have been developed for the management of vaginal candidiasis. Polymeric nanofibres consisting of the drug were formulated by electro spinning method. The resultant nanofibres were found to be effective offering sustained release of drug to treat vaginal infections. Electrospun solid dispersions of maraviroc were formulated and evaluated for constant intravaginal pre-exposure prophylaxis of HIV. The resultant solid dispersions have showed rapid release of maraviroc for the prevention of vaginal infections.

METHODOLOGY IN EVALUATION OF VAGINAL DRUG DELIVERY SYSTEM

A vaginal detailing must be assessed by performing both in *vitro* and in *vivo* examines. Contingent upon the measurement frame, extra tests for vaginal medication items may incorporate appearance, thickness, pH, molecule estimate examination, disintegration rate, content consistency and microbial points of confinement[93].

In vitro studies

In vitro studies include the determination of drug release and bio-adhesive characteristics in addition to various physical and chemical properties of formulations. The discharge attributes of a medication from a vaginal detailing can be resolved in recreated vaginal liquid (pH 4.2) and in different disintegration media (pH go 2–12) by various sorts of dispersion cells with specific adjustments and a vaginal disintegration analyzer .The bio-glue quality of the vaginal definition can be measured by different strategies (like Wilhelmy plate surface strategy).

***In vivo* studies**

In different animal models, *in vivo* studies are held for distribution, spreading, retention and to assess efficacy of formulations in the vagina. Assessing the distribution, spreading and retention of vaginal formulations in sheep and humans Gamma scintigraphy and colposcopy are desirable techniques. However, the significance of these findings is debatable. However Magnetic resonance imaging (MRI) and an intravaginal optic probe are the two techniques which are being developed to measure the degree of coverage in the vaginal vault. Various animal models such as sheep, rats, rabbits, rhesus monkeys, macaque monkeys, dogs and mice have been used in different studies in the development of vaginal formulations[93]. While white rabbits are used for primary irritation and sub chronic toxicity testing. Recently developed tissue model vaginal-ectocervical (VEC) will serve as a useful, highly reproducible, non-animal tools to assess the irritation due to vaginal care product.

CONCLUSION

Mucoadhesive vaginal drug delivery formulations offer potential improvements in residence time, bioavailability and penetration of drug through mucus membrane of vaginal cavity. It reduces the side effects that are caused by another route of drug administration like avoid first pass metabolism.

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Table 1: Influence of age on the variation of pH, length, and width of human vagina

Changes of vagina	pH	Length of vagina (cm)	Width of vagina (cm)
Before puberty	7	4.5-6	1-1.5
Reproductive age	4-5	10	2.5
Adult premenopause	4-5	7-8	2
Post-menopause	4-7	4.5-6	1-1.5

Table 2: The list of marketed vaginal products

Brand Name	Active Ingredients	Application
Replens®	Polycarbophil	Post menupousal atrophy[49]
Vagifem®	Estradiol hemihydrates	Vaginal atrophy
Zendol	Danazol	Endometriosis
Nonoxynol-9	Nonoxynol-9	Contraceptive
Nuvaring®	Etonogestrel/ethinyl estradiol	Contraceptive
Nestorone®	Ethinyl estradiol	Contraceptive
Gyne-lotrimin®	Clotrimazole	Vaginal yeast infections
Monistat®	Miconazole nitrate	Vaginal yeast infections
Crinone®	Progesterone	Infertility due to inadequate luteal phase
Trivagizole®	Clotrimazole	Vaginal yeast infections
Prochieve®	Progesterone	Progesterone deficiency
Meprate®	Medroxy progesterone acetate	Endometriosis