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Novel Concepts in Vaginal Drug Delivery

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ABSTRACT

The traditional vaginal drug delivery systems have limitations like poor bioadhesive properties; produce leakages, short residence time in the genitourinary tract and self-cleansing action of the vaginal tract. There is a need for the development of innovative vaginal formulation technology that fulfils certain criteria such as desirable product dispersion throughout the vagina, retention for intended intervals, and adequate release of drug and improvement of human reproductive health. With the advancement in pharmaceutical technology, the new vaginal drug delivery systems are taking the place of the traditional delivery systems such as pessaries, tablets, creams, foams, irrigations etc. Approaches used for the development of recent Vaginal Drug Delivery Systems include novel drug loaded inserts, hydro gel systems containing phase change polymers such as poloxamer exhibit sol–gel transition in response to body temperature, pH and specific ions, mucoadhesive drug delivery systems, liposome's, micro emulsion based vaginal gel, vaginal rings, cubic gels, formulations based on polystyrene and formulations based on silicone elastomers. The recent trend of research work is on nanoparticulate drug delivery through vaginal route. Novel approaches use applications other than the conventional contraception and vaginal infections, this delivery system can be used to treat cancer and to deliver various proteinaceous and peptide drugs. The potential exists for a much wider use of vaginal delivery systems than currently existing systems.

Keywords: *Mucoadhesive, Liposomes, vaginal rings, nanoparticles.*

INTRODUCTION

In this era of pharmaceutical research, the field leading is the development of novel drug delivery system for drug molecules which already exist so that their efficacy is maximised with better patient compliance and reduced adverse effects. With the advancement in technology of drug delivery there has been a wider choice of sites for drug administration. Vagina, as a site for drug delivery, has certain advantages due to which it has been exploited in order to achieve desirable therapeutic effects. The above said advantages are presence of dense network of blood vessels which makes it excellent route of drug delivery for both systemic and local effects. Others include its ability to by-pass first pass metabolism, ease of administration, low enzymatic activity, high permeability for low molecular weight drugs and this route provides for self medication continuously for weeks or months at a time with a single application resulting in better pharmacokinetic profiles.

The first formulation which was designed for vagina was to treat local bacterial, fungal infections and inflammations. With the development of novel products for female health, comprising therapeutic substances such as peptides, proteins, antigen there is need for designing high performance intravaginal drug delivery systems. This route provides a better alternative to the parenteral route for drugs like bromocriptine, propanolol, oxytocin, calcitonin, LHRH agonists, human growth hormone, insulin and steroids used in hormone replacement therapy or for contraception. The vagina serves as an excellent route for the delivery of hormonal contraceptives because of lack of drug interactions as observed in the gastrointestinal tract [1].

A formulation given by this route includes pessaries, tablets, inserts, cream, powders, douches, gel, vaginal rings etc but because of limitations like messiness, leakage and low residence time, there has been poor patient compliance and loss of therapeutic efficacy therefore more stress is laid on the development of Intra-vaginal controlled release drug delivery system which is an effective means of continuing delivery of therapeutically active agents. The foremost advantage of such dosage forms is maintaining them in the vagina for an extended period of time, resulting in lower dosing frequencies. The first controlled drug delivery system for use in the vagina was developed in 1970, which was a vaginal ring used for delivery of medroxy progesterone acetate for contraception.

Recently, the vaginal route has been explored as a novel route for the delivery of chemotherapeutic agents for treatment of all types of cancer.

Certain factors considered with reference to vaginal drug delivery system:

Vaginal Secretions: Though there are no goblet cells in vagina and hence it does not release mucin even then vaginal epithelium is considered as a mucosal surface, Vaginal discharge consists of a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, leukocytes, endometrial and tubal fluids. The cervical mucus contains inorganic and organic salts, mucin, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). The volume, viscosity and pH of vaginal fluid may have impact on vaginal drug absorption. The absorption of poorly water-soluble is increased when the fluid volume is higher [2]. Whereas presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from vaginal cavity and subsequently reduce absorption.

Vaginal pH: The vaginal pH of healthy women of reproductive age is acidic (pH 5 4–5); which is maintained by lactobacillus convert glycogen from epithelial cells to lactic acid. The changes in pH occur by factors such as age, stages of menstrual cycle, infections and sexual arousal. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase the pH [3]. The vaginal pH should be controlled for successful vaginal delivery of drugs.

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

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protein and peptide drugs in the vagina than the gastrointestinal tract.

Cyclic changes: The changes in hormone levels (especially estrogens) during the menstrual cycle lead to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions [4]. The variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes creates problem in achieving consistent drug delivery.

Advantages of Vaginal Drug Delivery Systems:

The vaginal drug delivery systems are now frequently used as they offer following advantages: [5, 6]

- This is a better delivery system in case of nausea and vomiting.
- Stomach and intestinal irritation can be avoided.
- Hepatic first pass elimination can be avoided.
- As there is no contact with digestive fluid so enzymatic degradation of drugs is avoided.
- Drug delivery can be stopped by removing the dosage form e.g. Vaginal rings.
- Rapid drug absorption and quick onset of action is achieved.
- When compared to parenteral medication in terms of patient on long term therapy, this system is convenient.
- The vaginal bioavailability of smaller drug molecules is good and in case of larger drug molecule it is improved by means of absorption enhancer.
- Self-medication is possible.
- It permits continuous and prolonged residence of the dosage form at the site of application.
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by other parenteral routes.
- The self-insertion and removal of the dosage form is possible.

Limitations: [7]

Apart from above mentioned advantages this route has several disadvantages too which is listed as follows:

- This drug delivery system is gender specific
- The vaginal route is less preferred because of inconvenience.
- The permeability of the vagina is strongly influenced by the estrogens concentration, which can influence the pharmacokinetics of drugs.
- The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) and this amount is decreasing with increasing age which can affect the vaginal absorption of drugs.
- The pH of the vaginal fluid is also a factor which affects the drug absorption as the unionized forms will be preferable absorbed.

Classification of Intra-Vaginal Drug Delivery System: [8]

- Vaginal Tablet
- Vaginal Powder
- Vaginal Capsule
- Vaginal Ointment
- Vaginal gel and creams
- Suppositories or Pessaries

Vaginal Tablets: [9]

The Vaginal tablets are same in composition as conventional oral tablets but it has the advantage of ease of manufacture and insertion.

The lactose based progesterone tablet can be used to deliver drug up to 24 hours and also can treat a variety of progesterone deficiency conditions such as menstrual irregularities, functional bleeding, luteal phase defects, and infertility.

Fig. 1: Vaginal Tablets

Sometimes Mucoadhesive polymers are used in formulation of vaginal tablet to increase vaginal residence time. Drugs that are administered as vaginal tablets include itraconazole, clotrimazole and prostaglandins.

Vaginal Ointments: [10]

Vaginal ointment consists of oil and an aqueous phase. Vaginal ointment mainly comprises drug such as alendronate, clodronate, tiludronate, pamidronate, etidronate, ibandronate, neridronate, residronate, zoledronate or olpadronate dissolved in the aqueous phase and the oil phase added and both phases are properly mixed.

Vaginal Creams and Gels: [11]

Vaginal Creams and gels are mainly used for topical delivery of contraceptives and anti-bacterial drugs. Metronidazole and clindamycin are the most commonly used vaginal cream for the treatment of bacterial vaginosis.

The main underlying principle behind vaginal creams and gels is that of emulsion or hydrogel based drug delivery. These hydrogels, when placed in an aqueous environment, swell and retain large volumes of water in their swollen structure and results in drug release in a controlled fashion. A swelling controlled release hydro gel delivery system for intravaginal administration of an antifungal drug, Miconazole has been reported.

A gel micro emulsion based formulation of a spermicidal with anti- HIV effect, a vinyl phosphate derivative of zidovudine, has been developed.

Drugs for cervical ripening and induction of labor are also available as a vaginal gel form. Oxytocin, dinoprostone and misoprostol are commonly used drugs for cervical ripening and induction of labor.

Fig. 2: Vaginal Cream

Vaginal Suppositories: [12]

This vaginal formulation also known as Pessaries are designed to melt in the vaginal cavity and release the drug for several hours.

These are now most commonly used to administer drugs for cervical ripening prior to childbirth and local delivery of drugs. Other drugs that are administered as suppository include dehydroepiandrosterone sulphate for ripening effect on the uterine cervix, Miconazole for vaginal candiasis and progesterone for hormone replacement therapy. The medicated pessaries have recently been used for delivery of prostaglandin E2 (PGE2) for ripening of the cervix and induction of labor.

Recent Advances in Vaginal Drug Deliery System:

Bioadhesive delivery systems: [13]

The Vaginal Dosage forms currently in use are tablets, creams, gels and suppositories which come with the disadvantages

of low retention to the vaginal epithelium, leakage and messiness and hence causing inconvenience to the patient. To compensate for these problems, bio adhesive drug delivery systems are taken into account.

In bio adhesive drug delivery system, bio adhesive molecules capable of delivering the active compound for an extended period at a predictable rate are incorporated into a formulation. The vagina is a most suitable site for bio adhesive formulations as the product absorbs moisture, becomes a gel and releases medication in a time-controlled manner.

Bioadhesive polymers that have been used for vaginal formulation include hydroxypropylcellulose, polycarbophil and polyacrylic acid.

A bioadhesive polycarbophil gel, ReplensR, is the available form in the market, which is used to retain moisture and lubricate the vagina. The formulation remains in the vagina for 2–3 days and maintains the vagina at healthy, acidic pH. Various peptide and protein drugs have also been administered via bioadhesive micro particulate vaginal delivery system. Hyaluronic acid based intravaginal delivery of calcitonin, a polypeptide used in the treatment of postmenopausal osteoporosis, have been a success for intravaginal administration of drugs for systemic effect.

In a recent study a new mucoadhesive vaginal dosage form for the antimycotic agent, clotrimazole, was developed by incorporating bioadhesive polymers viz. polycarbophyl hydroxypropylmethylcellulose and Hyaluronic sodium salt into suppositories made of semi synthetic solid triglycerides. These polymers hold the suppositories in the vaginal tract for a longer period of time without adverse effects, thereby prolonging the residence of the drug on the vaginal epithelium. The presence of these polymers largely modulated the behaviour of suppositories in terms of adhesive force, liquefaction time and residence of the drug in the application site.

Solid Polymeric Carriers: [14]

These are the specifically designed non-messy intravaginal drug delivery systems that can be used to generate a variety of controlled delivery profiles over periods ranging from several days to several months.
These are of Two Types:

i) Solid Hydrogels: [15] The gelation and retention of *in situ*-gelling vaginal formulations could be a landmark in improving the therapeutic efficacy of drugs. The phase changes polymers polyoxypropylene and polyoxyethylene are used to form thermo reversible gels when incorporated into aqueous solution.

Phase change polymers like poloxamer exhibit sol–gel transition in response to body temperature, pH and specific ions, and they prolong the residence time of the dosage form in the vagina. Formulations based on a thermoplastic graft copolymer have been developed to provide the prolonged release of active ingredients like nonoxynol, progestins, estrogens, peptides and proteins in a vaginal environment.

Non-aqueous solutions of the copolymer in hydrophilic excipients undergo in situ gelation in a short period of time after application. These in situ gelling liquid formulations can provide the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and retention owing to the formation of a mucoadhesive gel.

ii) Elastomeric Intravaginal Rings (IVR): [16] The vaginal ring is an innovative platform for the convenient delivery of hormonal agents. The vaginal ring is a torous or circular shaped device which is made up of silicone elastomers which owing to its elastomeric properties exert a slight tension on vaginal walls.

The factors governing the release rate from the ring are its design, solubility of drug in the elastomers and the molecular weight of the drug. For example: Very high release rates can be attained by using a high drug load at the ring surface whereas Moderate release rates may be attained by coating a homogeneous ring and If an even lower release rate is desired, the drug may be confined to a small diameter at the centre of the ring (core ring).

This innovative technology has the capacity to deliver a constant dose of drug intravaginally over an extended period of time in a single application, to deliver drugs such as medroxyprogesterone acetate, chlormadinone acetate, norethindrone, norgestrel, levonorgestrel to treat conditions such as eating disorders, depression, migraine headache, pain, obsessive compulsive disorders pre-menstrual dysphoric disorders (PMDD).

Advantages of vaginal rings includes its user controlled nature, do not interfere with coitus, does not require a daily intake of pills and allows continuous delivery of low dose steroids. They are approximately 5.5 cm diameter with a circular cross section diameter of 4–9 mm and the ring is inserted in the vagina.

The vaginal rings are of three types:

Matrix Type IVR: It is the simplest IVR device, manufactured by a single injection of an active elastomers mix that contains the drug homogenously dispersed throughout the polymer matrix. Drug release from these types of devices follow the typical First order pattern for matrix systems.

Reservoir type IVR: In the reservoir or core IVR, the drug is located within a centralised core that is surrounded by a drug free silicone sheath that acts as a rate controlling membrane for drug diffusion.

One of the main advantages of this type over matrix type is that the release characteristics can be readily modified, either by changing the thickness of the sheath layer or by varying the core length.

Reservoir rings are manufactured in following steps:

- A drug loaded core is first prepared either by injection moulding (for low drug conc. ≤ 30%) or by Extrusion (high drug conc., 30- 70%) of drug elastomers mix.
- The full cores may be cut into smaller core lengths depending on the required release rate.
- The cores are then encapsulated within silicone elastomers in two stages to produce the full reservoir ring.

Sandwich (shell) IVR: It is a reservoir type IVR and consists of a narrow drug containing layer located a fraction of millimetre below the outer surface of the ring and positioned between a non-medicated impervious central core and a non medicated outer rate controlling band. The position of the drug core close to the surface ensures that this is the best suited to the delivery of drugs having poor polymer diffusion characteristics.

Nuva Ring is the only combined contraceptive vaginal ring available in the US market. It is a flexible, transparent, contraceptive vaginal ring consists of two active components, etonogestrel and ethinyl estradiol. The ring releases 120 mg/day of etonogestrel and 15 mg/day of ethinyl estradiol over a 3-week period of use. Clinical trials show that Nuva Ring is an effective contraceptive ring with good cycle control and user acceptability.

FemringR and EstringR are estrogen releasing rings used for estrogen therapy. FemringR, which is made up of silicone elastomers, contains acetate derived of estradiol (hydrolysed to estradiol after insertion), which is placed in the vagina once every trimester. EstringR R is made of silicone polymers and when inserted in the vagina releases 7.5 mg of estradiol per day.

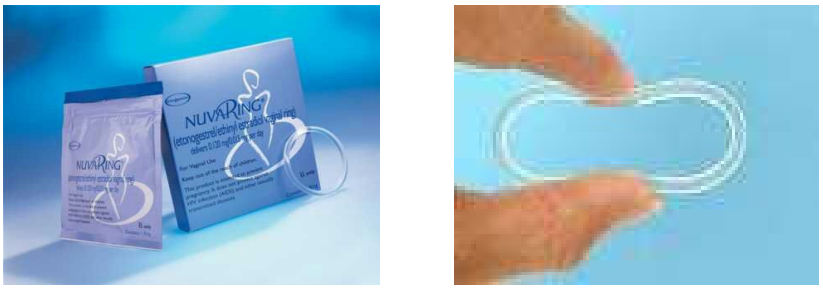

Fig. 3: Vaginal Rings

Vaginal Immunisation: [17]

Most of the conventional vaccines are administered via the oral or parenteral route resulting in systemic rather than mucosal immunity. Scientists have developed the successful immunization with DNA vaccines administered via various mucosal routes. Mucosal sites, mainly the vaginal route, represent the primary site of entry of pathogens into the human body. In addition the, mucosal immunization causes mucosal as well as systemic immunity. In this concern, several vaginal vaccine formulations are ongoing research against a variety of pathogens, including the human immunodeficiency virus (HIV). A recent study reports the development of a novel HIV-CCR5 receptor vaccine for the control of mucosal simian (SIV) and human forms of the virus. The vaccine, which targets both the virus and its CCR5 receptor, was administered in female rhesus monkeys either by the vaginal route or by targeting the proximity of the draining iliac lymph nodes. This immunization strategy through the vagina was found to significantly inhibit SIV/HIV infection in the animal model and shows promise for a novel approach in the prevention of HIV transmission.

DNA vaccines represent a new approach to the control of infectious diseases. An application of plasmid DNA vaccine to mucosal inductive tissues, including the vagina. The female genital tract has the capacity to produce humoral and cellular immune responses against locally encountered antigens. Vaginal immunization of rodents, human and non-human primates have been shown to elicit serum and secretory IgA and IgG responses in cervico-vaginal washes.

Table 1: List of Vaginal Preparations being developed or under development [18]

Preparation	Formulation	Active Ingredient
Advantage-S	Gel	Nonoxynol-9
CCVR (Combined Contraceptive Vaginal Ring)	Vaginal ring	3-ketodesogestrel ethinyl estradiol
Cleocin	Cream	Clindamycin Phosphate
Femstat One	Emulsion	Butaconazole
LASR Suppository	Pessaries	Nonoxynol-9
Efamast	Oil	Evening Promise Oil
Acyclovir	Liposomal Hydrogel	Acyclovir
Cotrimazole	Tablet	Cotrimazole

Applications of Vaginal Drug Delivery systems [19]

- This route is effective for vaginal immunization.
- Multi-cycle administration of vaginal contraceptive rings.
- Treatment or Prevention of Sexually transmitted diseases.
- Treatment of local fungal infection such as Candidiasis.
- Effective for the delivery of hormones.
- Delivery of peptides such as calcitonin for prevention of Osteoporosis.

CONCLUSION [20]

Despite of having so many advancements in the field of vaginal drug delivery systems, still this route is underutilised. Previously the formulations in the use for this of delivery were tablets, creams, gels, capsules, powders and Pessaries for use in contraception, vaginal infections, cervical ripening and labour induction. But now with the researches Bioadhesive formulations emerged as the suitable formulation for local and systemic drug delivery.

IVRs have also shown significant acceptance within female population. Researches are being carried on for further development of more sophisticated rings. The area which is still need to be discovered is the immunization through vaginal route and it has become more important with the increase in STDs patients. Further challenge is to treat cancer like disorders and to deliver various proteins and peptides through this route. Still there exist the potential for much wider use of vaginal drug delivery system. This review aims at the proper utilisation of vaginal route as an acceptable method for drug delivery.

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