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A REVIEW ON CURRENT STATUS OF VAGINAL DRUG DELIVERY SYSTEM

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ABSTRACT :

The vagina has been considered a potential route for drug delivery for centuries. The scientific community has recently directed its attention towards the development of effective and safe medication delivery methods for vaginal use, including vesicular systems, nanoparticles, microparticles, vaginal rings, microneedles, etc., An extensive summary of vaginal formulations and current advancements and trends in vaginal medication delivery is given in this article.

Keywords: Vaginal Formulation, Mucoadhesion, Novel formulation

Introduction:

The vagina, an integral part of the female reproductive system, presents numerous advantages over traditional drug delivery routes. These advantages include a substantial surface area available for drug absorption, comparatively low enzymatic activity, the avoidance of first-pass effects, relatively high permeability to a broad spectrum of drugs including proteins and peptides, and ease of administration. Administering therapeutic drugs designed for both local and systemic delivery can be accomplished effectively through the vaginal mucosa.[1]Traditional vaginal dosage forms, such as semi-solids, tablets, capsules, pessaries and liquid preparations are linked to certain health risks. Significant drawbacks such as poor retention, messiness, and leaking that make it difficult for users to use, which lowers patient compliance and reduces the effectiveness of such therapy.[2]Vagina also has special characteristics, such as a different pH, bacterial flora, hormonal cyclic fluctuations, permeability, and perfusion time. Thus, the effective administration of the medications via vagina poses a pharmaceutical difficulty. Vaginal drug delivery systems need to be developed and evaluated with these issues in mind. A carefully designed vaginal product relies on the vehicles that safely and efficiently distribute the medicine, or active pharmaceutical component, in a way that preserves the pharmaceutical agent.[3]

Ideal properties of vaginal drug delivery systems include,

- They should melt at vaginal temperature
- They shouldn't irritate the vagina and should be non-toxic
- They should have sufficient adhesion to maintain the drug for longer time for proper absorption and bioavailability
- They should have proper viscosity to increase residence time of drug.[4]

Anatomy and physiology of vagina:

Vagina is an important organ in the female reproductive tract. It is a tubular, long (10cm) fibromuscular canal lined with mucous membrane. The vagina has three layers: the internal mucosal layer, the intermediate muscular layer and the external tunica adventitia.[5] The presence of folds and micro-elevations on the surface of epithelial cells allows the vagina to expand and allow the stationing of vaginal formulation, increasing the surface area of the vagina and improving absorption of medicine. The vaginal squamous epithelial thickness may vary with the altered amount of estrogen in body. The vaginal mucosa contains large stores of glycogen, the decomposition of which produces organic acids and the resulting acidic environment retards microbial growth. Although it is not as rigid as the intestine and it does not have peristaltic motion, drug release, distribution, and absorption occur after vaginal delivery have a significant influence on vaginal administration. Vaginal fluid is kept at a pH of 3.8 to 4.2. Because vaginal transudate and ejaculate are both alkaline in nature, the pH of vaginal fluid may rise during the menstrual cycle. Age, health issues, menstrual cycle stage, estrogen levels, cervical mucus levels, and infections all affect pH levels. In comparison to the gastrointestinal tract, the human vaginal tract has less enzymatic activity, which results in less protein and peptide medicines breakdown in the vagina. The enzymatic activity of human genital tract is less when compared to gastrointestinal tract for less degradation of proteins and peptide drugs in vagina. [1]

Factors affecting vaginal drug delivery

Drugs are primarily transported across the vaginal membrane in three ways:

- First, transcellularly through concentration-dependent diffusion through the cells;

- Second, paracellularly through tight junctions; and
- Third, vesicular or receptor-mediated.

The absorption profile from vaginal drug delivery may be altered by factors related to physiology or formulation that impact the two main steps of drug absorption from the vaginal delivery system: drug dissolution in the vaginal lumen and membrane penetration.[6] Several factors can impact the absorption of drugs, including,

1. Physiological factors

The physiological factors affect vaginal drug delivery includes age, hormonal balance, pregnancy, pH fluctuations, microflora concentration, thickness and porosity of the epithelium, concentration of enzymes, production of vaginal fluid, the extent of vaginal discharge,etc., For example, vaginal epithelium thickness influences steroid absorption through the vaginal canal.[7] Vagina typically maintains a pH of 3.8–4.8 which get influenced by many factors such as presence of vaginal discharge and coitus frequency. Because of the relatively thin vaginal epithelium before puberty, drugs will be absorbed through the vagina more easily; however, during puberty, the thickness of the vaginal epithelium increases, which causes a decrease in drug absorption.[8]

- Vaginal pH

Lactobacillus converts glycogen from epithelial cells to lactic acid, maintaining the acidic pH of the vagina in healthy women of reproductive age. A number of variables, including age, menstrual cycle stages, diseases, and sexual excitement, can affect pH levels. Semen, cervical, uterine, and menstrual fluids all function as alkalizing agents to raise pH. Drug administration through the vagina should be successful if the pH of the vagina is regulated. Since many electrolytes are weak, variations in the vaginal pH will modify the degree of ionization and impact release profile of medications that are pH sensitive.[9]

- Micro flora

Since the vaginal microbiota competes with other micro-organisms for nutrients and secretes substances like lactic acid that make the vaginal environment unwelcoming to other potentially pathogenic microbes, it plays a crucial role in the health of the female reproductive system. The balance of the normal microbiota and the vaginal environment should therefore be taken into consideration when designing formulations for intravaginal delivery.[10]

- Cyclic changes

Alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH, and secretions were caused by changes in hormone levels, particularly estrogens, during the menstrual cycle. Endopeptidases and aminopeptidases have variable activity in response to hormonal fluctuations, which makes it difficult to provide consistent medication delivery.[9]

2. Absorption life-cycle:

The two main mechanisms involved in medicine absorption from vaginal delivery devices are drug dissolution in the vaginal lumen and membrane penetration.[11] Factors related to formulation that influence medication dissolution and membrane transport may have an effect on the absorption profile from the vagina.[12] For instance, the absorption of medications may be impacted by periodic changes in the thickness of the vaginal epithelium. While steroids and local estrogen seem to be more absorbed from thinner postmenopausal epithelium, progesterone appears to be better absorbed from thicker, more vascularized epithelium. [13,11,14] The microbial balance between other, mostly gram-negative anaerobes and lactobacilli, which dominate the flora, may also have an impact on drug absorption. Similar to this, variations in the volume and composition of vaginal fluid, pH, etc., might impact medication release. [15,16]

3. Pharmacological factors

Certain drugs results in increased vaginal epithelium thickness and a decrease in drug absorption. The properties of administering drugs also affects the vaginal drug absorption.[14]

Mechanism of drug absorption

Similar to other mucosal drug delivery pathways, there are several possible methods by which drugs can pass the vaginal barrier.
The three methods of diffusion are as follows:

a) Diffusion via the cell (transcellular route) caused by a concentration gradient;
b) Diffusion within the cell (intracellular route) mediated by vesicles or receptors; or
c) Diffusion through the tight junctions (paracellular or Intercellular route).[17]

There are two primary steps that the vaginal delivery system's drug absorption process follows:

- Dissolution of drug in vaginal lumen and
- The drug penetration.[18]

Vaginal formulations

Conventional vaginal drug delivery systems include, tablets, suppositories, gels, creams etc., Novel vaginal delivery systems avoid limitations associated with conventional systems. The novel formulations include vaginal rings, nanodroplets, insitu forming gel and bio adhesive delivery systems.

❖ **Conventional vaginal formulations**

- Vaginal tablets

Vaginal tablets are conventional vaginal formulation which are melt or dissolve in the vaginal cavity and release medication to the cavity. On vaginal administration, one must consider the changes brought on by hormonal fluctuations during menstruation and the post-menopausal cycle. The initial rate of medication absorption in women after menopause may be dramatically altered by the change in vaginal epithelial thickness and it can be considered during the formulation of a vaginal tablet. Their composition is similar to conventional tablets and they are more stable, can easily manufactured and easy to handle than other formulations.[19] Traditional vaginal tablets have a low adhesion and a brief residence period in the vaginal canal; nonetheless, in order to guarantee their effectiveness, numerous dosages must be administered. [20,21,23]

- Vaginal cream

Topical delivery of antifungal, antibacterial, and contraceptive medications is accomplished using vaginal creams. Applying vaginal creams can be messy, painful, and even embarrassing if the cream seeps into the undergarments. Additionally, the precise dosage is not given due to the formulation's uneven dispersion when applied vaginally. However, they are commonly used due to the availability and ease of application using an applicator. Vaginal creams cause irritation on vaginal mucosa due to its increased surfactant content and they may leak due to the lesser muco-adhesion. [24,25,]

- Vaginal gel

Vaginal gels can be easily applied, use continuously, non-invasive, economical and greater drug absorption is possible than other formulations.[41] Vaginal infections have been avoided by using vaginal gels. In addition, they can be utilized to lessen other sexual issues such discharge and vaginal irritation. Gels are utilized as a lubricant when vagina is dry. Vaginal gels have certain drawbacks, such as being restricted during pregnancy and menstruation.[26]

- Vaginal suppositories

Fig.1 vaginal suppository[42]

Numerous vaginal suppositories are available on the market that are intended to release antibacterial and antifungal medications into the vagina to treat various vaginal infections. Vaginal suppositories are said to have several benefits, such as self-administration, convenience of formulation, and avoidance of the first pass metabolism. There are further negative effects, such as messiness, decreased bioadhesion, contraindications during pregnancy, and other sexual issues.[26] Usually, these come in torpedo-shaped dosage forms, however oval shapes are preferable for vagina. Combinations of surfactants, preservatives, and different molecular weight polyethylene glycols are the most widely used base for vaginal suppositories. They are made to melt in the vaginal cavity and release the active ingredient over an extended length of time. They are buffered to an acidic pH. According to reports, suppository systems work well for delivering progesterone for hormone replacement therapy, antifungal medications for vaginal candidiasis, and medications for cervical ripening before childbirth.[27]

❖ **Novel formulations**

- Mucoadhesive vaginal tablet

The efficiency of conventional vaginal tablets is dependent on the administration of numerous doses due to their limited residence period in the vaginal canal and low adherence. Mucoadhesive polymers can increase adherence and extend residence time when added to vaginal tablets. Furthermore, these polymers hydrate to form hydrophilic matrices that alter or maintain the release of the active substances by eroding, expanding, or hydrating them. Vaginal mucoadhesive tablets are made with a variety of mucoadhesive polymers which are capable of withstanding the physiological changes occurring in vagina and have sufficient viscosity, swellability and sustained release properties. [20,21,22,23]

- Bilayer vaginal tablets

The widely used vaginal tablet formulation is inexpensive to produce, simple to insert into the vagina, and easy to make, which makes it a great option for use in underdeveloped nations. Bilayer vaginal pills often consist of two distinct layers of chemicals, each of which is meant to release the medications simultaneously for a synergistic effect. In some bilayer vaginal tablet one layer may intented for rapid drug release and the other layer will prolong the drug release. The major purpose of bilayer vaginal tablet is to prevent the chemical incompatibilities of different medicinal agents.[28]

- Fast releasing foaming vaginal tablets

An effervescent combination and a surfactant foaming ingredient are added to the formulation to create foaming vaginal tablets. Such formulations on administration increases the bioavailability of drug due to their ability to alter structure and physiology of vaginal mucosa. However, their limited stability

at high humidity necessitates certain preparation and storage conditions, which is a drawback. Because they prevent excessive lubrication and leaks from the vaginal cavity and enable for a consistent dose to be dispersed over the entire mucosal surface, foaming vaginal tablets are chosen as they ensure quick breakdown over a significant area.[29]

- Vaginal foam

Contraceptive foams, or vaginal foams, are used to delay or stop conception. Vaginal foam contains spermicide, which is added to destroy sperm and lower the likelihood of getting pregnant. Many drawbacks have been noted, including messiness, ineffectiveness against other sexually transmitted infections, potential for vaginal inflammation and discomfort, and the need to be used non conjunction with another contraceptive method for maximum effectiveness.[26]

- Microemulsion based vaginal gel

For the local and systemic administration of hydrophobic drugs, microemulsions have drawn a lot of interest. The microemulsions would increase the availability of hydrophobic medications to vagina. To prolong the contact of drug in the vaginal mucosa, the microemulsion is formulated as a gel using mucoadhesive polymers. By formulating to microemulsion based vaginal gel, the bioavailability of hydrophobic drugs can be improved to a greater extend.[30]

- Stimuli responsive insitu spray gel

To get around the drawbacks of traditional formulations for the topical delivery of medication, in situ spray gel formulation techniques are being investigated. Furthermore, these in situ spray gels demonstrate a prolonged release of the medication that was entrapped, resulting in a prolonged effect. However, the application of this in situ hydrogel is made very easy by the aqueous base, which will remain in a solution state prior to administration at room temperature (<30°C); in contrast, the formulation turns into a gel due to the presence of stimuli, such as pH or temperature at the application site.[31]

- Vaginal Microsphere Gel

In the pharmaceutical industry and other disciplines, microencapsulation is frequently used to conceal tastes or odours, extend the release of drugs, stabilise their components, increase bioavailability, and provide many dosage forms that may be controlled or targeted. In order to give longer drug release for vaginal infections such as vaginal candidiasis and vaginitis, vaginal microsphere gel is utilised. The microsphere incorporated mucoadhesive vaginal gel can used to deliver drugs for both local and systemic sites with advantages over conventional vaginal drug delivery systems.[32]

- Hydrogels

One of the most popular vaginal dose forms is a hydrogel, which has a moisturising effect, the right viscosity, longer residence time, and good distribution over the mucosal surface. They are simple to make and are well received by the patients. Because of its mucoadhesiveness, biodegradability, and antibacterial action against a variety of bacteria and fungi—all of which are highly significant, chitosan stands out among the many hydrogel-forming polymers. Numerous drug delivery nanosystems have been studied as a means of enhancing vaginal drug delivery with chitosan.[33]

- Solid-Lipid Nanoparticles Hybrid Gels

In place of phospholipid-based vesicle liposomes, solid lipid nanoparticles (SLPs) have become a more stable lipid-based nanosystem. SLPs can be created using easily accessible and stable lipids such cetyl palmitate, glyceryl monooleate, stearyl alcohol, stearic acid, and cetostearyl alcohol. For vaginal administration, adding an insoluble medication to SLPs can improve its permeability, surface area, and solubility.[25]

- Nanocrystal loaded insitu hydrogel

The science of drug delivery has shown increased interest in nanocrystals (NC) due to its high drug content and nanoscale. These characteristics appear to be appealing for vaginal compositions. Due of their great dispersion and thermodynamic instability, NCs require surface modification to stop potential particle growth. Meanwhile, surface modification can affect how well nanocrystals function in vivo. Nanocrystals can be used to deliver water insoluble drugs and by their modification it can prolong drug at the vaginal mucosa.[34]

- Vaginal rings

Fig.2. Vaginal ring[36]

Circular drug delivery devices called vaginal rings are intended to release the medication gradually once the ring is inserted into the vagina. Vaginal rings are made of flexible polymeric material and can be used to produce either localised or systemic effects. They provide the controlled release of medications over an extended period of time. A woman inserts the ring herself, either with or without the use of an applicator. Vaginal rings have a number of benefits, including regulated release, non-interference with coitus, continuous supply of modest doses of medication, and elimination of the need for daily pill consumption. Vaginal rings have many benefits, including controlled drug release, local application, safety, low side effects, and good patient compliance because of how infrequently they must be administered. However, because women differ in their needs, habits, preferences, and physical characteristics, these rings are manufactured with a fixed geometry at uniform sizes and doses are not preferrable.[35,36]

- Nanodroplets

Drug distribution in subcellular spaces is enhanced by nanodroplets. Here, chitosan-shelled nanodroplets (ND) have been developed for valacyclovir vaginal delivery using the desire to increase the drug's antiviral activity, sustain the release, and lengthen the retention period.[37]

- Vaginal film

Films are formed by incorporating drug in various film forming materials such as polymers and other ingredients like plasticizers, stabilizers and preservatives. These are usually thinner and may contain disintegrants which release drug rapidly at the site of action. Films have the properties of both gels and solid formulations and thus it is preferred. Vaginal films have advantages like rapid drug release, increased patient compliance due to its ease of application, convenience in carrying and its smaller size.[38]

- Vaginal sheets

Although the vaginal sheet is a type of vaginal film, it is not intended to breakdown instantly to release the medication. Specifically, this formulation needs to be larger and thicker than films and have the capacity to absorb vaginal secretions without quickly losing its structural integrity. Thus, the vaginal sheets produce a prolonged action in the vaginal mucosa.[39]

- Microneedles

Microneedles are tiny needles placed on a patch, which is employed to supply active ingredients. Water-soluble and biodegradable polymers make up dissolving microneedles (DMNs) in which the drug is incorporated. After being placed, the DMN would breakdown and allow the drug to be released in a controlled manner. Better drug loading and ease of manufacture are features of DMNs. Additionally, it is simple and convenient to apply. Several polymers, such as sodium hyaluronate, chitosan, sodium carboxymethylcellulose, poly(vinylpyrrolidone)/PVP, and PVA, have been utilised in the formulation of DMN. PVP and PVA have been used in DMN formulation in certain investigations. Both polymer combinations demonstrated adequate mechanical and insertion qualities. Their combination therefore offers sufficient penetration of active compounds. The use of DMNs for vaginal delivery has not received much attention, despite the possibility that it could enhance the distribution of an active ingredient in the vaginal tissue.[40]

Evaluations of vaginal formulations

It is necessary to carryout invitro and invivo evaluations of vaginal formulations. The physicochemical characterization is carried out based on the nature of dosage forms.

- *Invitro* evaluations

In vitro investigations are used to determine the physical and chemical properties of formulations as well as medication release and bio-adhesive qualities. Drug release properties from vaginal formulations can be assessed using a dissolution tester and several kinds of diffusion cells with specific modifications, in simulated vaginal fluid (pH 4.2) and different dissolution media. Several methods such as the Wilhelmy plate surface technique can be used to test the bio-adhesive strength of the vaginal formulation.

- *Invivo* evaluations

To evaluate the effectiveness, dispersion, spreading, and retention of formulations in the vagina, in vivo investigations are carried out in a variety of animal models. The optimal methods for determining where it is located, dissemination, and retention of vaginal formulations in humans and sheep are gamma scintigraphy and colposcopy. The importance of these findings is questionable, though.

An intravaginal optic probe and magnetic resonance imaging (MRI) are two imaging modalities being developed to assess the level of covering in the vaginal vault. To create vaginal formulations, researchers have used a variety of animal models, including mice, rats, rabbits, rhesus monkeys, dogs, and sheep. For tests on subchronic toxicity and primary irritation, white rabbits are employed. Tissue models for the vagina and ectocervical (VEC) will be helpful, highly repeatable, and non-animal instruments for evaluating irritation brought on by vaginal care products.[4]

Conclusion

The vaginal route is a potentially effective way to give medications for both systemic and local illnesses. Most vaginal formulations on the market were designed for localized administration of medication exclusively. There should be more thorough research done on the systemic distribution of medications through the vagina. The novel formulation avoids many of the restrictions of conventional vaginal formulations. More advanced research should be done to deliver medications through the vagina with more bioavailability and less discomfort.

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