ABSTRACT: Vagina is one of the effective route for drug administration like contraceptives steroids, anti-retroviral, metronidazole etc. Ranges of drug delivery system suitable for intra vaginal administration are hydro gels, suppositories, pessaries and intra vaginal rings. Mucoadhesive microsphere contain important part of particulate drug delivery system because of their small size and effective properties. Mucoadhesive microsphere play a major role in novel drug delivery system. Mucoadhesive microsphere is an ideal targeting system with high security profile. review article provide the information about theories of mucoadhesive, mechanism of mucoadhesion. It also provides various method of preparation of mucoadhesive microsphere.

KEYWORDS: Vagina, mucoadhesive microsphere, intra vaginal drug delivery, mucoadhesion.

I. INTRODUCTION

Vagina is administrated for contraceptives, antifungal and antimicrobial. It is used for local or system absorption. The vaginal wall is suited for absorption of drug for the systemic use. A vagina contains vast network of blood vessels. Vaginal cavity is a essential area of the reproductive tract and acts as site for drug administration of vaginal discharge. According to changes in the female reproductive organ, female are highly prevent to fungal infection. The pH of vagina from 3.5-5 in normal adult female and natural lactic acid produced by micro flora of vagina is responsible for maintaining the pH. Sometimes it is alkaline in nature in presence of semen (pH 7 to 8). Reproductive tract infection is a major public health issues are seen in world and especially in developing countries. According to WHO 357 million cases of reproductive tract infection transmitted sexually throughout the world. Vaginal formulations such as suspension, crems and solutions are incapable to maintain effective drug concentration for extended period of time inside the vaginal cavity due to their small resident time at the site of administration.

1.1 Advantages of drug delivery system:-
- Minimum systemic adverse effect.
- Increases it’s bioavailability.
- Fast onset of action.
- First pass metabolism can be deducted.
- Self medication is determined.
- Extend release.
- Use less total drug than the oral dose.

1.2 Disadvantage of drug delivery system:
- Gender selectivity.
- Patient inflexibility.
- Some drug can be administrated by vaginal route.
- Few drugs are sensitive at vaginal pH.
- Variability of vaginal absorption related with menstrual cycle, menopause, and pregnancy.
- Impact with sexual intercourse.

1. VAGINAL ANATOMY AND PHYSIOLOGY WITH RESPECT TO DRUG DELIVERY SYSTEM

The vagina is an fibrous muscular tube generally 10 cm in length consist of three different layers named as,
- Outer adventitious layer,
- Middle muscularis layer,
- Inner mucosal layer.
The vaginal physiology is mainly impacted by age, hormonal balance, pregnancy, pH changes, and concentration of micro flora. Major changes can be observed in vaginal physiology with age, like thickness of epithelium layer, production of vaginal fluid, etc.

The vaginal rugae and micro ridges on the epithelial cell surface allow vaginal expansion, permit the position of vaginal formulation and enhance the surface area of the vagina so increases the drug absorption. The vagina have noticeable features in terms of vaginal secretion, pH, enzyme activity, and microflora. Those factors influence formulation spreading and maintain absorption and drug release in vagina.

### 2.1. Vaginal secretion

The vagina discharge is a composite of many secretions that gather in the vagina from peritoneal, follicular tubal, uterine, Bartholin's, and Skene's glands. In presence of moisture, solid dosage formulations have optimally dispersed in the vaginal canal quickly after intercalation to avoid disturbance to the users.

### 2.2. Enzyme activity

The certain enzymatic activity of four different amino peptidase in vaginal homogeneously reduces in the order of Sheep > guinea pig > rabbit > human > rat. The human genital tract have smaller enzymatic activity leading to less degradation of protein and peptide drug in the vagina than the GIT.

### 2.3. Vaginal pH

A healthy woman's genital tract is acidic (pH 3.5-4.5) and is maintained within the scale by bacteria converting glycogen from epithelial cells to lactic acid.

### III. FACTORS AFFECTING VAGINAL DRUG ABSORPTION

1. Transcellular by concentration sub-ordinate diffusion by the cells,
2. Paracellularly mediated through tight junction,
3. Vesicular transfer as identified by Richardson and illum.

Absorption of drug from vaginal drug delivery system present in 2 steps:
1. Drug dissolution in vaginal lumen and
2. Membrane penetration.

The biological or formulation factor that influence drug dissolution and membrane transport can potentially influence the absorption profile from Vaginal drug delivery system. The many factor and process are associated in drug absorption from the vaginal route.

### 3.1. Physiological factor

Vaginal absorption of steroids is affected by thickness of vaginal epithelium. Vidarabine drug shows 5-100 times excessive permeability coefficient throughout the starting dioestrous stage than across the oestrus stage in guinea pig. Vaginal absorption of estrogen is observed higher in postmenopausal woman than premenopausal women. Vaginal absorption of steroids is affected by thickness of vaginal epithelium and the epithelial thickness because of their reduced long term estrogen therapy. The absorption of progesterone is increased with increasing vascularity of the vagina. After cervical mucus of the vagina it is a glycoprotein gel. It could be possible for bioadhesive drug delivery system. The presence of cervical mucus plays a permeability barrier to prospective drug candidate.

The volume, viscosity, and pH of vaginal fluid provides a either positive or negative impact on vaginal drug absorption. The absorption poorly water-soluble drug are increased with increase in volume of fluid. In Many drugs weak electrolytes and pH are the factor change their degree of ionization and affect the absorption of the drug. The change in vaginal pH affect the release profile of pH sensitive drug from Vaginal drug delivery system.

### 3.2. Physicochemical Properties of drug

Molecular weight, lipophilicity, ionization, surface charge, chemical nature are the physicochemical Properties they can affect on vaginal drug absorption. Example: vaginal permeability of straight chain aliphatic alcohols enhances because of chain length dependent manner. Vaginal permeability is higher in lipophilic steroid than hydrophilic steroid. The low molecular weight lipophilic drugs are highly absorbed than large molecular weight lipophilic or hydrophilic drug. The study on vaginal absorption of polyvinyl alcohol recommend that the molecular weight check before the compound are not absorbed may be higher for vagina than other mucosal surface. A vaginal fluid consist of large amount of water, any drug deliberate for vaginal drug delivery system required certain degree of

solubility in water. The human vaginal permeability to drug with various physicochemical Properties is very restricted, much more work to do on the effect of physicochemical parameters of drug on Vaginal absorption18.

IV. MECHANISM OF MUCOADHESION

The mechanism of mucoadhesion is split into two stages

1. Contact stage
2. Consolidation stage

The contact stage is identify the contact between the mucoadhesive and the mucous membrane with expanding and inflammation of the formulation, initiating, it produce deep contact with the mucous membrane19. Each steps can be facilitated by the nature of the dosage form and how it is administered20.

4.1. Theories of mucoadhesion

- **Electronic theory**
  It involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electron between the mucoadhesive polymer and mucin glycoproteins network21.
  Example – Positively charged polymer chitosan and negatively charged mucosal surface interaction with them becomes adhesive on hydration and provide a contact between a dosage form and absorbing tissue.

- **Wetting theory**
  It states that if the contact angle of liquid on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. Suppose two such substrate surface in contact with each other in the presence of light, the liquid acts as adhesive between the substrate surface22.

- **Adsorption theory**
  Initial contact between two surface, materials is adhered because of surface force acting between atom in two surface. Two types of chemical bond such as primary chemical bond of covalent nature and secondary chemical bond that is van der walls force, electrostatic force, hydrogen and hydrophobic bond these forces used to eminent their bonds23.

- **Diffusion theory of mucoadhesion**
  It describe the polymeric chain are formed from bioadhesive interpenetrated into glucoprotein mucin chain and extend adequate depth within the opposite matrix to to allow formation of a semi permanent bond24.

V. METHOD OF PREPARATION OF MUCOADHESIVE MICROSPHERES

A. **Polymerization:**
   It includes the reaction of monomeric subunit at the interface between core material substance and a continuous phase which is core material is dispersed. Continuous or core material are the supporting phases it is generally a Liquid or gas thus polymerization occurs at liquid-liquid, liquid-gas, liquid-solid, or solid-gas interface.

B. **Pan coating:**
   In these method the coating material is applying as a solution or atomizer spray to the desired solid core material applied to the coating pan. Warm air is move to coated material to remove the solvent.

C. **Phase inversion method**
   It involves combination of drug into dilute polymeric solution in methylene chloride and resultant mixture is discharge into an uncompassionate with strong non solvent like petroleum ether in a ratio of 1:100 carried to spontaneous manufacturing of microcarriers in the range of 0.5mm to 5.0mm. Microcarriers produced by clarified and washed with non-solvent such as petroleum ether25.

D. **Coacervation**
   It consist 3 steps performed under continuous agitation. Three steps mainly contain formulation of 3 immiscible chemical phases, deposition of coating, rigidization of the coating. Immiscible phases consist of a liquid manufacturing vehicle, core material phase and a coating material phase. Microencapsulation can be prepare by phase separation method, in these method changing the temperature of polymer solution by changing the pH of medium, by adding a salt or non solvent to the Polymer solution by promoting polymer polymer interaction26.
E. Hot melt Microencapsulation
It was the first method used to prepare microspheres of polyanhydride from sebacic acid. The polymer is firstly melted and then solid drug particles are added with continuous mixing. The mixture is dipped in non-miscible solvent like silicon oil while stirring and heated slightly exceeding the melting point of polymer. The emulsion is stabilized, cooled, filtered, washed with petroleum ether. The disadvantage of this method is to moderate temperature to the drug is exposed.

F. Spray drying
These methods include dissolving or dispersing the drug in the polymer solution which is then spray dried. In these methods, the size of microsphere can be managed by the rate of spraying, feeding rate of polymer solution, nozzle size, and drying temperature.

G. Solvent removed
These are non-aqueous methods of Microencapsulation. It is suitable for water labile polymer such as polyanhydride. It includes dissolving polymer into volatile solvent like methylene chloride and the drug is dispersed or dissolved in it. The mixture is dipped in silicon oil containing span 85 and methylene chloride. After that petroleum ether added it stirred until solvent extracted into oil solution.

H. Solvent evaporation
It is the most widely used method of Microencapsulation. A buffered solution of drug with a stabilizing agent is poured into an organic phase of the polymer solution in Chloroform with vigorously stirring to form water in oil emulsion. The microspheres are washed, centrifuged and lyophilized to get free flowing and dried microspheres.

I. Ionotropic gelation
In these methods, microspheres are formed by dissolving gel type polymer, such as alginate in a solution dispersed in pure water mixed thoroughly to form a smooth viscous dispersion. Microspheres are made by extracted through needle or sprayed to a hardening solution containing calcium chloride stirred at low speed for 30 min to complete reaction to produce rigid microspheres.

VI. DRUG LOADING TECHNIQUE IN MICROSPHERE
The drug are loaded in microspheres mainly using two methods,
A) During the preparation of the microsphere
B) After the preparation of the microsphere by incubating them with the drug solution.

The active component of drug loaded by physical entrapment, chemical linkage, surface absorption. It includes many other processes such as presence of additives, method of preparation, heat of polymerization, agitation, intensity etc. The loading of drug after preparation of microsphere performed incubating them with high concentration of drug in suitable solvent. The drug may be loaded in the microspheres through penetration or diffusion of the drug via the pores present in the microsphere as well as by absorption.

VII. CHARACTERIZATION

1. Percentage Yield
The formula for calculating the percentage yield of each batch was calculated by the formula:

\[
\text{Percentage yield} = \left( \frac{\text{Total weight of dried microspheres}}{\text{Drug added} + \text{chitosan weight} + \text{TPP weight}} \right) \times 100
\]

2. Particle Size Determination by Optical Microscopy
All the prepared eight batches can be analyzed for particle size determination using optical microscope. A hundred particles each were counted and average particle diameter was found out by using the formula:

\[
\text{Average particle diameter} = \frac{\sum n \times d}{N}
\]

Where, \( n = \) total no. of particles in that size interval
\( d = \) Diameter of the particles of that size range
\( N = \) total no. of particles.
3. Drug Content & Encapsulation Efficiency
This can be performed using UV absorption method. After recording the absorbance, the drug content and encapsulation efficiency were calculated by the formulae mentioned below.

\[
\text{Calculated amount of drug} = \frac{(\text{Abs - intercept})}{\text{slope}} \times 100
\]

\[
\text{Drug content} = \frac{\text{Calculated amount of drug}}{\text{Total amount of microspheres}} \times 100
\]

\[
\text{Encapsulation efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100
\]

4. Swelling Index
Swelling index demonstrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption, which is a primary requirement for initiation of mucoadhesion. Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, a weighed amount of mucoadhesive microsphere was placed in 100 ml of buffer and allowed to swell. At predetermined time intervals the swollen microspheres were removed from the media and the excess surface adhered liquid drops were removed by blotting and weighed by using microbalance. The microspheres then dried in an oven at 60 °C for 5 hr until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula

\[
\text{Percentage swelling index} = \frac{(\text{Mass of swollen microspheres} - \text{Mass of dried microspheres}) \times 100}{\text{Mass of dried microspheres}}
\]

5. In Vitro drug release
\text{In-vitro} release profile of drug from the mucoadhesive microspheres was examined in dissolution media using standard IP/BP/USP dissolution test apparatus (rotating basket or paddle type). To carry out the test, microspheres equivalent to 100 mg of drug were dispersed in dissolution media that is similar to the fluid present at the absorption site as per monograph and maintained at 37±2 °C under continuous stirring at 50 rpm. An aliquot of 5 ml was withdrawn through a hypodermic syringe fitted with a 0.4 μm Millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically after suitable dilution. The released drug content was determined from the standard calibration curve of given drug

6. Stability studies of microsphere
The success of an effective mucoadhesive microspheres were evaluated only through stability studies that were aimed to obtain a stable product which assures its safety and efficacy, and peak profile up to the end of shelf life, at prescribed storage conditions. The preparation was divided into 3 groups and placing the microspheres in screw capped glass container. The containers were stored at ambient humidity conditions, 4°C (refrigerator), room temperature and 40°C±2°C (thermostatic oven). After 15, 30 and 60 days drug content of all the formulation were analyzed using spectrophotometrically

7. Accelerated Stability Studies for the Mucoadhesive Vaginal Microspheres
The selected P8 microspheres were subjected to accelerated stability studies for 6 months at 40 °C ± 2 °C /75% ± 5% RH.

8. Ex vivoBioadhesion Studies
The \text{ex vivo} evaluation of the mucoadhesive properties of the microspheres was carried out using cleaned vaginal tissue obtained from a freshly slaughtered sheep from slaughter house. The percentage mucoadhesion was then calculated by using the formula:
VIII. CONCLUSION

Vaginal route acts superior for the delivery of therapeutically important molecules such as microbicides, novel mucoadhesive vaginal drug delivery system includes vaginal tablet, vaginal films, vaginal cream, gels, suppositories or pessaries. This novel delivery system beneficial for improving female health. Microsphere provides protection, masking, reduction in dissolution rate, spatial targeting to the active ingredient. Microspheres are ideal targeting drug delivery system with high safety profile.

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