



e-ISSN: 2319-8753 | p-ISSN: 2320-6710

IJRSET

International Journal of Innovative Research in
SCIENCE | ENGINEERING | TECHNOLOGY

INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 10, Issue 5, May 2021

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA

Impact Factor: 7.512

9940 572 462

6381 907 438

ijirset@gmail.com

www.ijirset.com



Vaginal Mucoadhesive Microsphere

Shailee Tiwari*, Shraddha Paturkar

Department of Pharmaceutical Chemistry, Durgamata institute of Pharmacy, Parbhani, Maharashtra India

*Correspondence

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 vessels¹. 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)². 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 world³. Vaginal formulations such as suspension, creams 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 its 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 intercourse⁴.

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

The vagina is a fibrous muscular tube generally 10 cm in length consist of three different layers named as,

- Outer adventitious layer,
- Middle muscularis layer,
- Inner mucosal layer⁵.



The vaginal physiology is mainly impact by age, hormonal balance, pregnancy, pH changes, and concentration of micro flora. Major changes can 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 to vaginal expand, permit the position of vaginal formulation and enhanced 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 influences formulation spreading and maintain absorption and drug release in vagina.

2.1. Vaginal secretion

The vagina discharge is a composite of many secretion that gather in vagina from peritoneal, follicular tubal, uterine, Bartholin's and Skene's glands⁶. In presence of moisture, solid dosage formulation have optimally disperse in the vaginal canal quickly after intercalat 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 degradable of protein and peptide drug in the vagina than the GIT.

2.3. Vaginal pH

A good health women genital tract is acidic (pH 3.5- 4.5) and is continue within the scale by bacteria converted into glycogen from depilation cells to lactic acid⁷.

III. FACTORS AFFECTING VAGINAL DRUG ABSORPTION

1. Trans cellular by concentration sub-ordinate diffusion by the cells,
2. Paracellularly mediated through tight junction,
3. Vesicularly mediated transfer as identified by Richardson and Illum⁸.

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 on drug dissolution and membrane transport can be potentially influences 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 affect by thickness of vaginal epithelium⁹. Vidarabine drug shows 5-100 times excessive permeability coefficient throughout the starting dioestrous stage than across the oestrus stage in guinea pig¹⁰. Vaginal absorption of estrogen are observed higher in postmenopausal woman than premenopausal women¹¹. Vaginal absorption of steroids is affected by thickness of vaginal epithelium and the epithelial thickness because of their reduced long term estrogen therapy¹². The absorption of progesterone are increased with increase vascularity of the vagina¹³. After cervical mucus of the vagina it is a glycoproteins gel¹⁴. 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 to 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 system¹⁵.

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 manner¹⁶. 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 surface¹⁷. 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 liquid, 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 vanderwalls 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 glucoproteinmucin 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. Microcapsule can be prepared 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 first melted and then solid drug particles are added with continuous mixing. The mixture is dipped in a non-miscible solvent like silicon oil, stirred, and heated slightly exceeding the melting point of the polymer. The emulsion is stabilized, cooled, filtered, washed with petroleum ether. The disadvantage of this method is that the drug is exposed to moderate temperature²⁷.

F. Spray drying

This method includes dissolving or dispersing the drug in the polymer solution which is then spray dried. In this method, the size of the microsphere can be managed by the rate of spraying, the feeding rate of the polymer solution, the nozzle size, and the drying temperature²⁸.

G. Solvent removed

This is a non-aqueous method of microencapsulation. It is suitable for water-labile polymer such as polyanhydride. It includes dissolving the polymer into a 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 is added and it is stirred until the solvent is extracted into the oil solution²⁹.

H. Solvent evaporation

It is the most widely used method of microencapsulation. A buffered solution of the drug with a stabilizing agent is poured into the organic phase of the polymer solution in chloroform with vigorous stirring to form a water-in-oil emulsion. The microspheres are washed, centrifuged, and lyophilized to get free-flowing and dried microspheres³⁰.

I. Ionotropic gelation

In this method, microspheres are formed by dissolving a 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 extracting through a needle or spraying to a hardening solution containing calcium chloride, stirred at low speed for 30 min to complete the reaction to produce rigid microspheres³¹.

VI. DRUG LOADING TECHNIQUE IN MICROSPHERE³²

The drug is 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 the drug loaded by physical entrapment, chemical linkage, surface absorption. It includes many other processes such as the presence of additives, method of preparation, heat of polymerization, agitation, intensity, etc. The loading of the drug after preparation of the microsphere is performed by incubating them with a high concentration of the drug in a 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:

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

2. Particle Size Determination by Optical Microscopy

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

$$\text{Average particle diameter} = \frac{\sum n * d}{N}$$

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.

$$\text{Calculated amount of drug} = \frac{\left(\frac{\text{Abs} - \text{intercept}}{\text{slope}} \right) (*10 * 100)}{1000}$$

$$\text{Drug content} = \frac{\text{Calculated amount of drug}}{\text{Total amount of microspheres}} * 100$$

$$\text{Encapsulation efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} * 100$$

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

$$\text{Percentage swelling index} = \frac{(\text{Mass of swollen microspheres} - \text{Mass of dried microspheres}) * 100}{\text{Mass of dried microspheres}}$$

5. In Vitro drug release

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 vivo Bioadhesion Studies

The *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:



$$1 - \frac{\text{Initial no. of microsphere - Microspheres remaining attached at T 60 min}}{\text{Initial attached microsphere}} * 100$$

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.

IX. ACKNOWLEDGE

The authors are thankful to teaching and non teaching staff of Durgamata Institute of Pharmacy.

REFERENCES

1. Kamel A.E., Solar M., Naggar V. & Gamel S.A., chitosan and sodium alginate based bioadhesive vaginal tablets, *AAPS Pharm Sci.*, 2002, 4(4): 1-7.
2. Kumar L., Reddy M., Shirodkar R., Pai G., Verma R., Preparation and characterization of fluconazole vaginal films for the treatment of vaginal candidiasis. *Indian Journal of Pharmaceutical Science.* 2013., 75(5): 585.
3. Yidana z., Boadu F., Adu- Gyasi D, et.al. vulvovaginal candidiasis, bacterial vaginosis and trichomoniasis in pregnant women attending clinic in the middle belt of Ghana, 2019., 19(1): 341.
4. Chang J.Y., Oh V.K., Kong H.S., Kim E.J., Jang D.D., Nan K.T., and Kim C.k., Prolonged Antifungal effect of clotrimazole containing mucoadhesive thermosensitive gel, *J. Control. Release*, 2002, 82, 39-50.
5. Kamel A.E., Sokar M., Naggar V., and Gamel S.A., Chitosan and sodium alginate based bioadhesive vaginal tablets, *AAPS Pharm Sci.*, 2002, 4(4): 1-7.
6. Francois M., Snoeck E., Putteman P., Wouter F., Proost E.D., Deluet U., Peeter J. & Brewster M.E., A mucoadhesive, Cyclodextrin based Vaginal Cream formulation itraconazole, *AAPS Pharm Sci.*, 2003, 5, 1-5.
7. Nelson A.L., The vagina : New Options for the administration of medications, *Medscape Today*. 2004, section 6 of 10.
8. Richardson J.L., Lillum., Routes of drug delivery, case studies (8) The vaginal route of peptide and protein drug delivery, *Advanced drug delivery. Review* 8(1992): 341-366.
9. Woolfson A.D., Malcolm R.K., Gallagher R., Drug delivery by the intravaginal route, *Crit. Review. Their drug carrier system.* 17(2000): 509- 555.
10. Durani M.J., Kusai A.F.H. Topical vagina drug delivery in the guinea pig, Inductive Effect of estrous cycle on the vaginal membrane permeability of vidarabine, *Int.J.Pharm.* 24(1985): 209- 218.
11. Pschera H., Hjerpe A., Carlstrom K., Influence of the maturity of the vaginal epithelium upon the absorption of vaginally administered estradiol-17-beta and progesterone in postmenopausal woman, *Gynecol. Obstet. Invest.* 27 (1989): 204-207.
12. Carlstrom k., Pschera H., Lunell N.o., Serum levels of estrogens, progesterone, follicle stimulating hormone and sex hormone binding globulin during simultaneous vaginal administration of 17-beta- oestradiol and progesterone in the pre and post- menopause, *Maturitas* 10 (1988): 307-316.
13. Villanueva B., Casper R.F., Yen S.S.C., Intravaginal administration of progesterone, enhanced absorption after estrogen treatment, *Fertil.Steril.* 35 (1993): 385-401.
14. Katz D.F., Dunmire E.N., Cervical mucus problems and opportunity for drug delivery via the vagina and cervix, *Advanced drug delivery, Review*, 11(1993): 385- 401.
15. Woody J., Bioadhesion new possibilities for drug adhesion? *Clinical pharmacokinetic*, 40(2001): 77-84.
16. Hwang S., Wada E.O., Yotsunangi T., Suhardja I, Higuchi W.I., Systems approach to vaginal delivery of drugs, 2 In situ Vaginal absorption of unbranched aliphatic alcohols, *J. Pharm. Sci.* 65(1977): 1574-1578.
17. Brannon- Peppas L., Novel vaginal drug release applications, *Advanced drug delivery. Review*, 11(1992): 169-177.
18. Sanders J.M., Matthews H.B., vaginal absorption of polyvinyl alcohol in Fisher 344 rats, *Human Exp. Toxicol.* 9(1990): 71-77.



19. Hangestrom H., Edsman K., Stromme M., Low frequency dielectric spectroscopy as a tool for studying the compatibility between pharmaceutical gels and mucus tissue, *Journal of pharmaceutical sciences*, 2003, 92, 1869-1881.
20. Lee J.W., Park J.H., Robinson J.R., Bioadhesive based dosage forms -The next generation, *Journal of pharmaceutical science* 2002, 89, 850-866.
21. Park J.B., Acrylic bone cement in vitro and in vivo property -structural relationship a selective review., *Annals of biomedical Engineering*, 1983, 11, 297-312.
22. Smart J.D., The basics and underlying mechanisms of mucoadhesion, *advanced drug delivery reviews*, 2005, 57, 1556-1568.
23. Robinson J.R., Leung S., Binding of acrylic polymers to mucin surfaces – structure property relationship, *critical Reviews in therapeutic drug carrier system*, 1998, 5, 21-67.
24. Zia H., Rhodes C.T., Mucoadhesive drug delivery systems, *drug development and Industrial pharmacy*, 1993, 19, 143-194.
25. Chickening D., Jacob J., Mathiowitz E., (Polyfumaric - co-sebacic) microsphere as oral drug delivery systems, *Biotechnology*, 1996, 52, 96-101.
26. Naredo K., Samel P.K., Meena K.P., Dangi J.S., Recent advances in microsphere manufacturing technology, *International Journal of pharmacy and technology*, 2011, 3(1): 854-855.
27. Mathiowitz E and Langer R., “polyanhydride micro spheres as drug carrier”, *Hot melt Microencapsulation . J.control*, 1987, 5, 13-22.
28. Bodmeier R., Chen H., Preparation of biodegradable polyanhydride (9) lactide micro particles using a spray drying technique, 1988, 40, 754-757.
29. Carino P.G., Jacob J.S., Chen C.J., Hertzog B.A. “ Bioadhesive drug delivery system of Fundamentals, Novel drug approaches and development”, *Marcel Dekker, New York*, 1999, 459.
30. Ogawa Y., Yamamoto M., Okado H., Yashiki T., Shimamoto T. *Chem. Pharm.* 1988, 36, 1095-1103.
31. Mathew S.T., Moy A.C., Mathapan R., Microsphere an overview . *International Journal of pharmaceutical and Biomedical sciences* 2011, 2(2): 332-338.
32. Belagamwar V., Shah V., Surana S.J., Formulation and evaluation of oral mucoadhesive multiparticulate system containing metoprolol tartrate ., *In vitro- ex vivo characterization, current drug delivery*, 2009, 6(1): 113-121.



INNO  **SPACE**
SJIF Scientific Journal Impact Factor

**Impact Factor:
7.512**

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA



INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

 **9940 572 462**  **6381 907 438**  **ijirset@gmail.com**



www.ijirset.com

Scan to save the contact details