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A brief review on unani mucoadhesive vaginal drug delivery system

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Abstract
In almost all classical and current Unani literature, various Unani Drug Dosage Forms, such as *hamool, marham, zimad, natool* etc. have been mentioned for the treatment of pelvic inflammatory diseases, besides oral medication. There is no concept of any vaginal tablet in the classical and/or current Unani literature. The recent advancements in the field of conventional pharmaceutics led to develop mucoadhesive vaginal tablet as a sustained release dosage form. It has many advantages over existing Unani classical dosage forms, such as mucoadhesive vaginal tablet provides to control both drug release and permanence time in the application area, drug release at asustained rate with the possibility of maintaining it in the vagina for extended periods of time and easy insertion, i.e., user-friendly application. In order tocomply with the patient compliance, ease of administration without intervention of medical personnel, high efficiency based on an even distribution and long retention time of the drug in the vagina, simple to making, no irritation, and free of discomfort to the user must be considered in an ideal intravaginal drug delivery system. Thus, there is a felt-need to design and develop a new dosage form in such a way to get maximum efficacy and easy to apply, i.e., user-friendly. This review paper summarizes mucoadhesive vaginal drug delivery system.

Keywords: mucoadhesive vaginal drug delivery system, unani drug dosage forms, vaginal tablet, unani vaginal tablet, vaginal drug delivery

1. Introduction
The Unani tib is a holistic stream of medicine which is a part and parcel of medical diversity of India. Unani system of medicine deals with protection promotion of health and prevention of diseases, if disease occurs, it has potential to manage and / or treat the disease / disorder. The half of population comprised of women is suffering from common health problems mostly due to negligence and injustice. The most common ailment *inter alia* is *waram-e-rahem* in the form of pelvic inflammatory disease (PID).Based on a variety of sources, it is estimated that more than 50% of reproductive age women have had one episode of PID. Sometimes multiple episodes of PID lead to hospitalization. There is no permanent cure of PID available in the conventional medicine. The standard protocol of its treatment has antibiotics, anti-inflammatory and analgesic agents causing temporary relief with a lot of side effects and recurrence too.

In Unani classical literature, various Unani Drug Dosage Forms (UDDFs), such as *hamool, marham, zimad, natool* etc. have been mentioned for the treatment of *warm-e-rahem* (pelvic inflammatory diseases), besides oral medication. Some classical UDDFs are administered through the vaginal route by dissolving it into *arq* or *aab* of any single drug, such as *arq-e-Makoy* or freshly prepared *aab-e-Makoy sabz, aab-e-Kasni sabz* etc. This medicated water is soaked in a piece of cotton/cloth and placed inside the vagina in the form of *hamool*. The entire application happens to be very cumbersome and devoids of any sustained effect. A large quantity of drug drains out from the vagina, and leaves lesser amount to exert any therapeutic effect. There is another popular dosage form, such as tablet (*qurs*), which is exclusively used orally. No concept of any tablet used externally as a vaginal tablet (*qurs-e-mahbil*) has been mentioned in the classical and/or current Unani literature. Thus, there is a felt-need to design and develop a new dosage form in such a way to get maximum efficacy and also easy to apply, i.e., user-friendly.

The recent advancements in the field of conventional pharmaceutics led to develop mucoadhesive vaginal tablet as a sustained release dosage form. It has many advantages over existing Unani classical dosage forms, such as mucoadhesive vaginal tablet provides to control both drug release and permanence time in the application area, drug release at a sustained rate with the possibility of maintaining it in the vagina for extended periods of time and easy insertion, i.e., user-friendly application.The wall of vagina is very suitable for absorption of drug for systemic use, due to its vast network of blood vessels, rich flow of blood and better permeability.

2. Demerits of existing classical Unani dosage form
- The application of formulations, namely *marham, hamool, natool etc.* used with cotton/cloth may cause erosion and irritation of vaginal mucosa leading to further aggravating the situation.
- Wastage of drug due to spilling from vagina.
- A potential threat of infection transfer through material.
- Once inserted medicated cotton/cloth in the vagina, needs to be removed.

- The entire procedure is very cumbersome.
- Its application is also not a user-friendly.
- It has a delayed effect due to erratic absorption.

Hence, there is a need to design and develop an alternate, effective, safe and user-friendly means to replace these classical dosage forms.

3. Mucoadhesive delivery system

Mucoadhesive is defined as the ability of a material (mucoadhesive polymer) adhering to the mucosal layer. By the interfacial forces, they are held together for an extended period. The mucosal layer is made up of mucus which is secreted by the goblet cells (glandular columnar epithelial cells) and is a visco-elastic fluid. It lines those visceral organs which are exposed to the external environment [1].

3.1 The Mucoadhesive drug delivery system has the following main advantages over the existing solid and semi-solid preparations:

- The formulation provides to control both drug release and permanence time or duration of action in the application area.
- Rapid mucoadhesion, prolonged residence time in the vaginal cavity even in absence of physiological secretions associated with a controlled drug delivery, extended dosing interval.
- Due to increase of drug contact, daily administration of drug shall be reduced.
- The vaginal tablet has sustained effect for a longer duration.
- It allows self-insertion, thereby, user friendly.
- It is an acceptable and preferable form of drug delivery system for gynecological problems.
- Non-sticky and stable in extremes of temperature and humidity.
- Socially, culturally, and economically acceptable.
- Avoidance of local irritation phenomena.
- Rapid mucoadhesion, prolonged residence time in the vaginal cavity even in absence of physiological secretions associated with a controlled drug delivery, extended dosing interval.
- Low production cost [2-6]

3.2 The mechanism of mucoadhesion is generally divided into two (2) stages

3.2.1 The contact stage

This stage is characterized by the contact between the mucoadhesive polymer and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.

3.2.2 The consolidation stage

In this stage, the mucoadhesive polymers are activated by the presence of moisture. Then moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak vander Waals and hydrogen bonds [7].

3.3 Theories of mucoadhesion

The mucoadhesive mechanism is very complex to understand and there are six (6) theories to understand its mechanism, are given below:

a. The electronic theory
b. The wetting theory
c. The adsorption theory
d. The diffusion theory
e. The mechanical theory
f. The cohesive theory

The electronic theory proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces. The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces. The adsorption theory proposes the presence of intermolecular forces, viz., hydrogen bonding and Vander Waal's forces, for the adhesive interaction amongst the substrate surfaces. The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure. The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion. The cohesive theory proposes that the phenomena of mucoadhesion are mainly due to the intermolecular interactions amongst like-molecules [8].

3.4 Mucoadhesive Polymers

Mucoadhesive delivery systems are being explored for localization of the active agents to a particular location/ site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Mucoadhesive polymers are water-soluble and water-insoluble. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

All three polymer types can be used for drug delivery [9].

3.5 Mucoadhesive agents

The adherence is promoted through mucoadhesive agents by permitting a close contact of formulation with the vaginal mucosal surface. The mucoadhesive agents include polycarbophil, hyaluronic acid, chitosan, sodium alginate, tragacanth, carbomer, acacia, sodium carboxymethyl cellulose or other cellulose derivatives, carbopol 974P-NF, carbopol 971P-NF, carbopol-940, HPMC and other co-polymers of acrylic acid. Xanthan gum and sodium alginate show site-

specific bioadhesive properties in a simulated vaginal environment [9].

4. Vaginal anatomy, histology & physiology

The vagina is a fibro-muscular tube, it connects the cervix (the opening of the uterus) and the vulva which plays a major role in reproduction. It is longer on the posterior wall (around 9 cm) than anteriorly (approximately 7.0 cm). The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface. The vault of the vagina is divided into four (4) fornices, posterior, anterior and two lateral.

As shown in the following figure, it connects the cervix (the opening of the uterus) and the vulva (the external genitalia).

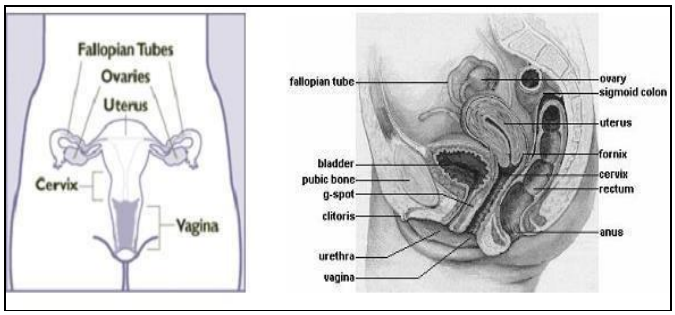

Fig 1: Schematic drawing of the vagina

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

Changes of vagina pH	pH	Length of vagina (in cm)	Width of vagina (in cm)
Before puberty	7	4.5-6.0	1.0-1.5
Reproductive age	4-5	10.00	2.50
Adult pre-menopause	4-5	7.0-8.0	2.00
Post-menopause	4-7	4.5-6.0	1.0-1.5

It is positioned between the rectum, bladder and urethra. The vagina is a slightly S-shaped fibro-muscular collapsible tube and its dimensions range from 8.4 to 11.3 cm in length and 2.1 to 5.0cm in diameter. The vaginal wall consists of three layers, viz., the epithelial layer, the muscular coat and the tunica adventia. The main blood supply to the vagina is through the vaginal branch of the uterine artery. The vaginal mucosa has no goblet cells but it secrets a large amount of fluid containing enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids and alcohols. The enzymatic activity in the vagina is comparatively lower than in the gastrointestinal tract, but there is still a wide range of enzymes present in vagina, such as nucleases, lysozymes and esterases. Women of reproductive age produce fluid at a rate of approximately 6 mL/day, with 0.5-0.75 mL continually present in the vagina. The discharge produced by postmenopausal women is reduced by 50% compared to that produced by women of reproductive age. At the time of ovulation, mucus secretion increases, and it becomes clear, thin and alkaline. At other times the mucus produced is scanty and viscous [10-17].

The ecology of the vagina is influenced by factors, such as pH, hormonal levels and trauma during sexual intercourse, birth-control method, age and antimicrobial treatment. In the vaginal microflora, *Lactobacillus* (Döderlein's bacilli) is the most prevalent organism together with other facultative and obligate aerobes and anaerobes. The vaginal pH of healthy women of reproductive age is acidic. Lactic acid produced from glycogen by the *Lactobacillus acidophilus* present in the vagina acts as a buffer to maintain the vaginal pH between 3.8 and 4.2. As listed in Table above, the pH changes with age, stages of menstrual cycle, infections and sexual arousal. During menstruation, the pH of vaginal fluid is comparatively higher. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase pH. The pH of vagina increases at a higher level (5-7) in case of any infection or inflammatory disease, i.e., Pelvic Inflammatory Disease (PID), Metritis (*waram-e-rahem*), Cervicitis (*waram-e-fam-e-rahem*) [18].

5. Drug delivered through vagina follows two routes

i) Intravaginal route (vaginal mucosa to vaginal epithelium)
ii) Transvaginal route (vaginal mucosa to uterus and systemic circulation)

Vagina has specific blood flow property, portal type circulation, venous and lymphatic channels, which allow bypass the gastrointestinal tract absorption and liver detoxification and permit the transport of drug molecules from the vagina to the uterus and systemic circulation [19-21].

6. Advantages of vaginal drug delivery system

- Prolong action
- Minimize the systemic side effects
- Enhance the bioavailability of drug
- Avoid the first pass metabolism by liver
- Self medication possible
- Fast onset action
- Prolong residence of the drug on the site of application

7. Mucoadhesive vaginal drug delivery systems can be categorized as follows

- Mucoadhesive tablet
- Mucoadhesive gel
- Mucoadhesive film
- Emulsion type mucoadhesive system
- Pessary or Suppository

7.1 Survey of vaginal formulations available in the Indian market: physicochemical characterization of selected products

Indian vaginal products are available in several different dosage forms. Tablets are marketed most frequently (38%), followed by gels (15%) and creams (15%) [22].

In comparison to all other mucosal membranes, the vaginal mucosa offers the advantage that drug delivery systems can remain for the longest time period at the site of application. It provided the basis for the development of novel more effective vaginal formulations guaranteeing prolonged residence times.

7.2 Unani mucoadhesive vaginal tablet

The Unani mucoadhesive vaginal tablets are prepared using powdered Unani ingredients and mucoadhesive polymers, such as carbopol-940, HPMC, polycarbophil, cellulose ethers, chitosan and sodium alginate. A matrix mixture including the pharmaceutically acceptable excipients is used in the preparation of vaginal mucoadhesive controlled release matrix tablet. Diffusion of drug through swollen polymers and progressive erosion / dissolution of the gel matrix are the bases of drug release mechanism. Addition of soluble and insoluble fillers in the dosage forms and their weight ratio is responsible to detect the controlled release properties of vaginal tablets [23-25].

8. Conclusion

Various Unani Drug Dosage Forms, such as *hamool, marham, zimad, natool* etc. have been mentioned in almost all classical and current Unani literature for the treatment of pelvic inflammatory diseases, besides oral medication. No concept of any vaginal tablet in the classical and/or current Unani literature has been mentioned. The recent advancements in the field of conventional pharmaceutics led to develop mucoadhesive vaginal tablet as a sustained release dosage form. It has many advantages over existing Unani classical dosage forms, such as mucoadhesive vaginal tablet provides to control both drug release and permanence time in the application area, drug release at a sustained rate with the possibility of maintaining it in the vagina for extended periods of time and easy insertion, i.e., user-friendly application. In order to comply with the patient compliance, ease of administration without intervention of medical personnel, high efficiency based on an even distribution and long retention time of the drug in the vagina, simple to making, no irritation, and free of discomfort to the user must be considered in an ideal intravaginal drug delivery system. Therefore, development of Unani mucoadhesive vaginal tablet is an alternate, effective, safe and user-friendly dosage form to overcome the demerits of these classical dosage forms.

9. Conflict of Interest

There is no conflict of interest.

10. References

1. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in Mucoadhesive Drug Delivery System: A Brief Note. Designed Monomers and Polymers, 2009; 12:483-95.
2. Acarturk Fusun. Mucoadhesive vaginal drug delivery systems. Recent patent on drug and formulation, 2009; 3:193-205.
3. Valenta C. The use of mucoadhesive polymers in vaginal delivery. Adv Drug Deliv Rev. 2005; 57:1692-1712.
4. Knuth K, Amiji M, Robinson JR. Hydrogel delivery systems for vaginal and oral applications. Formulation and biological considerations. Adv Drug Deliv Rev. 1993; 11:137-167.
5. Robinson JR, Bologna WJ. Vaginal and reproductive system treatments using a bioadhesive polymer. J Control Release. 1994; 28:87-94.
6. Brannon-Peppas L. Novel vaginal drug release applications. Adv Drug Deliv Rev. 1993; 11:169-177.
7. Hogerstrom H, Edsman K, Strwmme ML. Frequency dielectric spectroscopy as a tool for studying the compatibility between pharmaceutical gels and mucus tissue. Journal of Pharmaceutical Science. 2003; 92:1869-81.
8. Harsulkar AA, Sreenivas SA, Mandade RJ, Wakada RB. Polymers in Mucoadhesive Drug Delivery System- A Review. International Journal of drug formulation and research. 2011; 2(3):61-67.
9. Patil SB, Murthy RSR, Mahajan HS, Wagh RD, Gattani SG. Mucoadhesive Polymers: Means of Improving Drug Delivery. Pharma Times. 2006; (38):25-8.
10. Vermani K, Garg S. The Scope and Potential of Vaginal Drug Delivery. Pharmaceutical Science and Technology Today. 2000; 3:359-364.
11. Goldberg DM, Hart DM, Watts C. Distribution of Enzymes in Human Vaginal Fluid: Relevance to the Diagnosis of Cervical Cancer. Pub Med. Gov. 1968; 21:964-973.
12. Valenta C. The use of Mucoadhesive polymers in vaginal delivery. Advanced Drug Delivery Reviews. 2005; 57:1692-1712.
13. Pendergrass PB, Belovicz MW, Reeves CA. Surface Area of the Human Vagina as Measured from Vinyl Polysiloxane Casts. Gynaecologic Obstetric Investigation. 2003; 55:110-113.
14. Bernkop-Schnürch A. Mucoadhesive Polymers. In: Dumitriu S (eds): Polymeric Biomaterials. Marcel Dekker. New York, 2002, 147-165.
15. Muir GG. Multiple Enzyme Studies in the Vaginal Fluid In Relation to Benign and Malignant Gynaecological Conditions. British Journal of Cancer. 1966; 20:448-462.
16. Wagner G, Levin RJ. Vaginal Fluid. In: Hafez ESE, Evans TN (eds): Human Reproductive Medicine: The Human Vagina. North Holland Publishing, New York, 1978, 121-137.
17. Justin-Temu M, Damian F, Kinget R, Van Den Mooter G. Intravaginal Gels as Drug Delivery Systems. Journal of Women Health. 2004; 13:834-844.
18. Jeffcoate N. Principles of Gynaecology. Edition IVth. Butterworth and Company. London. 1983; 21-24:303-328.
19. Muraleehdara KK, Santhil Kumar SK, Parthiban S. Mucoadhesive vaginal drug delivery system: A review on advance status. International Journal of Pharmaceutical Research & Analysis. 2013; 3(1):33-46.
20. Dodou D, Breedveld P, Wieringa P. Mucoadhesive in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm. 2005; 60:1-16.
21. Brache V, Croxatto H, Kumar N. Effect of sexual intercourse on the absorption of levonorgestrel after vaginal administration of 0.75mg in Carraguard gel: A randomized, cross-over, pharmacokinetic study. Contraception. 2009; 79:150-154.
22. Garg S, Vermani K, Kohli G, Kandarapur R, Tambwekar K, Garg A *et al*. Survey of Vaginal Formulations Available on the Indian Market: Physicochemical

Characterization of Selected Products. International Journal of Pharmaceutical Medicine. 2002; 16(3):141-152.
23. Hussain A, Ahsan F. The vagina as a route for systemic drug delivery. J Control Release. 2005; 103:301-313.
24. Perioli L, Ambrogi V, Pagano C, Scuota S, Rossi C. FG90 chitosan as a new polymer for metronidazole mucoadhesive tablets for vaginal administration. Int J Pharm, 2009; (in press)
DOI 10.1016/j.ijpharm.2009.05016Puri, R., Zhang Y., Foreman, P.B.: EP1757267 (2007).
25. Keshari SC, Kumar NP, Kumar SD. Intravaginal drug delivery system: An overview. American Journal of Advanced Drug Delivery. 2013; 1(1):043-055.