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Design & development of Unani Mucoadhesive vaginal tablet: An innovative approach

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Abstract
The most common gynecological ailment is *waram-e-rahem* in the form of pelvic inflammatory disease (PID) in more than 50% of reproductive age women. In almost all classical and current Unani literature, various Unani Drug Dosage Forms (UDDFs) have been mentioned for the treatment of *warm-e-rahem* and they have found various disadvantages. Thus, a new dosage form was designed to overcome disadvantages of existing Unani dosage form. The ingredients of Unani Mucoadhesive Vaginal Tablet (UMVT) were Tukhm-e-Khatmi (*Althaea officinalis*), Tukhm-e-Kanocha (*Phyllanthus maderaspatensis*), Tukhm-e-Katan (*Linum usitassimum*), Tukhm-e-Hulba (*Trigonella foenum-graecum*), Tukhm-e-Makoy (*Solanum nigrum*), Asapghol (*Plantago ovata*) and Murdarsang (*Plumbi monoxidum*). The UMVT was prepared by wet granulation method and evaluated for organoleptic characteristics and other physico-chemical properties, such as weight variation, thickness or diameter, friability, pH of 1% and 10% solutions, hardness disintegration time, dissolution time. The weight determined as per Indian Pharmacopoeia (IP) 2007 was 1000 mg. The UMVT had thickness of 0.6 cm and optimum compactness was found. The mean value of pH 1% & pH 10% of UMVT were 5.67 ± 0.15 and 5.77 ± 0.15, respectively. The mean value of hardness test and disintegration time test of UMVT were 1.73 ± 0.3 and 0.027 ± 0.0058, respectively. The highest Swelling Index of UMVT was found having sodium alginate and chitosan. *In vitro* mucoadhesive test on UMVT showed the highest mucin binding.

Keywords: unani mucoadhesive vaginal tablet (UMVT), *waram-e-rahem*, pelvic inflammatory disease (PID), mucoadhesive drug delivery system

1. Introduction
The half of population comprised of women is suffering from common health problems mostly due to negligence and injustice. The equity in health is still an unmet goal of Government. The most common ailment is *waram-e-rahem* in the form of pelvic inflammatory disease (PID). It is one of the causes of chronic pelvic pain, infertility, ectopic pregnancies. It is potentially a preventable disease. Generally, PID is not a reportable disease in India and precise figures on its prevalence are not available in all National Family and Health Surveys-I, II, III & IV (NFHSs). Based on a variety of sources, it is estimated that more than 50% of reproductive age women have had one episode of PID. 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 almost all classical and current Unani literature, various Unani Drug Dosage Forms (UDDFs), such as *hamool, marham, zimad, natool* etc. have been mentioned for the treatment of *warm-e-rahem*, besides oral medication. The Unani classical term *warm-e-rahem* denotes inflammatory condition of all parts of uterus, viz., fundus, corpus, cervix and internal os. Pathologically, the most affected part happens to be cervix, caused by a host of factors, such as injury from tampons, pessaries, IUDs, infection, hormonal imbalance etc. This clinical situation can be successfully mitigated by means of UDDFs employed as internal and external route of drug administration. 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.

Hence, an innovative strategy had been made to design and develop a user-friendly dosage form for *waram-e-rahem*. In this study, Unani Mucoadhesive Vaginal Tablet (UMVT) was developed to overcome the disadvantages of existing dosage

form. The aim of the present study was to formulate and evaluate a Unani mucoadhesive vaginal tablet for *in situ* application. The formulation contains seven [7] Unani single (*mufradat*) drugs which happened to be the ingredients of *Marham-e-Dakhiliyoon* (MD) were selected for design and development of UMVT. Because MD had been mentioned as an effective formulation in *warm-e-rahem* in almost all *qarabadeen* (pharmacopoeias) by Buqrat, Jalinoos, Rabban Tabari, Al-Razi, Al-Majoosi, Ibn Sina, Ibn Nafis, Jurjani etc. The ingredients of the formulation were tukhm-e-Khatmi (*Althaea officinalis*), tukhm-e-Kanocha (*Phyllanthus maderaspatensis*), tukhm-e-Katan (*Linum usitassimum*), tukhm-e-Hulba (*Trigonella foenum-graecum*), tukhm-e-Makoy (*Solanum nigrum*), Asapghol (*Plantago ovata*) and Murdarsang (*Plumbi monoxidum*). The uniqueness of this formulation lies in the fact that it is the one of the Unani classical formulations which has been used as such, i.e., without any alteration and addition.

2. Materials and Methods

2.1 Preformulation Studies

All drugs for the preparation of vaginal tablet were procured from the open market. All ingredients were inspected with unaided eyes for the presence of impurities and foreign matter, and which were removed. All drugs were dried under shade to remove the moisture. Samples of all drugs were separately packed in aseptic airtight plastic packing and sent for identification. The identity of all the drugs (excluding *Murdarsang*) was established by the experts at Raw Material Herbarium & Museum, CSIR-National Institute of Science Communication and Information Resources (NISCAIR), New Delhi. *Murdarsang* was identified by the experts from Department of Geology, AMU, and Aligarh.

2.2 Preparation of Unani Mucoadhesive Vaginal Tablet as Per Standard Operating Procedure (Sop)

2.2.1 Isolation of Mucilage from *Aspghol, Hulba, Katan,* and *Khatmi*

The four (4) ingredients of test formulation, namely *Aspghol, Hulba, Katan,* and *Khatmi* were taken in quantity of 100 grams each for isolation of mucilage. Each drug was soaked in distilled water (DW) for a period of 48 hours, and boiled for 10-15 minutes for complete release of mucilage into DW. The resulting mass of each drug was squeezed through muslin cloth. The acetone was added in an equal volume to the filtrate to precipitate the mucilage of each drug. The isolated mucilage was dried in an oven at 40°C for 2 hours. The dried mucilage of each drug was made powder by passing through sieve no. 80, and finally stored in desiccators, separately [1, 2].

2.2.2 Isolation of Mucilage from *Kanocha's* Seeds

Hundred (100) grams of *Kanocha*'s seeds were taken and soaked in DW for 15 minutes to complete release of mucilage into DW. The soaked seeds were blended for 15 minutes and filtered by muslin cloth. The filtrate was precipitated in the equal amount of acetone. The isolated mucilage was dried in an oven at 40°C for 2 hours. The dried mucilage was made powder by passing through sieve no. 80, and was stored in desiccator [3].

2.2.3 Extraction of *Makoy* Seeds

Makoy's seeds, one more ingredient of the formulation, were taken in the amount of 30 grams and extracted through soxhlet apparatus for a period of 6 hours. The extract was not properly dried. Thus, 10% of lactose anhydrous powder was added to the extract, and dried on water bath. The dried mucilage of the drug was made powder by passing through sieve no. 80, and stored in a desiccator.

2.2.4 Powdering of *Murdarsang*

Hundred (100) grams of *Murdarsang* was taken, and pounded in mortar and pestle. It was powdered by grinding and sieving through sieve no. 120, and was packed in a well closed air tight container [4].

2.2.5 Tablet Making by Wet Granulation Method

The all powdered ingredients as mentioned below in Table, excepting *Murdarsang* were mixed in ratio of 1:1 whereas *Murdarsang* was added in the ratio of 1:3. A starch solution of 5% was added into powder to make dough. In order to make granules, the dough was passed through sieve no.16. The granules were dried in the oven at the temperature of 55°C for a period of 2 hours [5].

2.2.6 Unani Mucoadhesive Vaginal Tablet (Sodium Alginate + Chitosan)

Nine hundred (900) grams of mucilage powder of all drugs was taken. Starch and talc were added in 10% and 5%, respectively. The magnesium streate was added as per need. Sodium alginate and chitosan were added in the quantity of 0.75 mg each. The tablets in oval shape were made by wet granulation method.

2.3 Evaluation of Physico-Chemical Parameters of Unani Mucoadhesive Vaginal Tablets (UMVTs):

The test versions of Unani Mucoadhesive vaginal tablet (UMVT) were subjected for the following physico-chemical parameters:

2.3.1 Organoleptic Characteristics:

The appearance was recorded according to the consistency of the formulation whether solid or semi-solid. The color of the UMVT was recorded under sunlight and examined for odor by slow and repeated inhalation of air over the material. Its shape was examined by visual observation.

2.3.2 Quality Control Test / Physical Characterization:

- **Weight Variation Test**

The percentage of weight variation indicates the uniformity of the dose as well as formulation using wet granulation method of tablet preparation. The die taken for making tablet was of 1 gram volume. The average weight was calculated and maximum % deviation was found. The mean weight variation should not vary by more than 5% of tablet weight [4, 6].

- **Thickness / Diameter**

The Tablet thickness is a function of the die fill and compression force. The thickness of UMVT was determined by using Vernier Calliper.

- **Friability**

Friability test can be performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The friability test apparatus consists of a plastic chamber divided into two parts which revolves at 25 rpm. A fixed number of tablets were weighed, placed in the tumbling chamber and rotated for four minutes of 100 revolutions. During each revolution the tablets fell from a distance of six inches to undergo shock. After 100 revolutions the tablets were again weighed. The loss in weight indicated the friability. The method was applied on UMVT.
The friability (f) is calculated by the formula as under:

$$f = 100\,(1 - \frac{wo}{w})$$

Where,
w_o = initial weight of the sample before friability test,
w = weight of the samples after friability test.

- **Determination of pH**

To determine of **pH of 1% solution,** 1 gram of UMVT was dissolved in 100 ml of water, and filtered individually. The pH of 1% solution was checked with a standardized glass electrode [7].
For determination of pH of 10% solution, 10 grams of UMVT was dissolved in 100 ml of water, and filtered individually. The pH of 10% solution was checked with a standardized glass electrode [7].

- **Hardness**

The hardness can be defined as the strength of the tablet to withstand the pressure applied on it. The tablet to be tested was held between a fixed and a moving jaw of Monsanto Hardness Tester. The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet broke out. The reading was noted from the scale which indicated the pressure required to break the tablet. It is generally expressed in Kg/cm^2. The Hardness Test was carried out on UMVT.

- **Determination of Disintegration Time**

The device is to test disintegration uses 6 glass tubes that are open at the top with a 10 mesh screen at the bottom end. To test for disintegration time, one tablet was placed in each tube, and the basket rack was positioned in a 1-L beaker of water, buffer solution at 37 ± 2°C was taken in such a manner that the tablet remained 2.5 cm below the surface of liquid on their upward movement not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. According to the test, ten (10) tablets of UMVT were disintegrated, and readings were noted, accordingly. All particles passed through the mesh screen in the time specified. If any residue remains, it must have a soft mass [6, 8, 9].

- **Dissolution Time**

The drug release rate was determined using USP dissolution apparatus-II (Basket apparatus). The dissolution vessels were filled-up to 1000 ml with various dissolution media maintaining the pH of 6.0, and the temperature was maintained at 37 ^{0}C ± 0.5^{0}C with stirring speed of 25 rpm. Various dissolution media were tried due to inability of release of drug from UMVT in DW (distilled water). Hence, the citrate buffer of pH of 6.0 was replaced with addition of 50 ml of methanol. The addition of methanol did better drug release from test formulation (UMVT). After addition of tablets in dissolution media, 5 ml of sample was withdrawn at 0. 30,1, 2, 4 and 8 hours for UMVT. The sample was analyzed individually using UV spectrophotometer.

- **Swelling Study**

The swelling behavior of tablet is described as the water absorbing capacity. The test UMVTs were weighed individually, and initial weight was considered as W1 and placed separately in Petri-dish containing 15 ml of buffer (pH 6.0) solution. UMVTs were completely immersed in the buffer solution. At the regular intervals (0.5, 1, 2, 3, 4), UMVTs were carefully removed from the Petri-dishes, and excess surface water was removed carefully using the filter paper. The swollen tablets were then re-weighed (W2). The experiment was performed in triplicate. The degree of swelling (water uptake) was calculated according to the following equation [10]:

$$\text{Swelling index (SI)} = \frac{W2 - W1}{W1} \text{ X } 100$$

Where,
W1 = Weight of dry tablet
W2 = Weight of wet tablet

- ***In Vitro* Mucoadhesive Study**

The procured mucin was dissolved in buffer 6.0 for making 2.5% of solution. The UMVT was evaluated for mucoadhesion property. The glass slides were washed, cleaned and dried. A line was marked in each glass slide for tablet placement. 0.5ml of prepared mucin solution was added on glass slide and tablet was placed on it, waited for 30 seconds to bind the mucin with excipients of tablets which was responsible for mucoadhesion. After 30 seconds, the glass slide of each tablet was lift up with steady motion keeping base of the slide fixed. The height from the working table was measured at the moment where the tablet started their movement with increasing inclination of the slide. The height of slide was recorded at the position where tablet started movement. Higher the height of movement showed higher mucoadhesive strength [11, 12].

- **Determination of Microbial Load**

For total bacterial count, total fungal count and presence of *E. coli*, *Salmonella*, *S. aureus* and *pseudomonas* was carried out by Shree Krishna Analytical Services, New Delhi. The test on UMVT was evaluated as per Quality Control Manual for Ayurvedic, Siddha and Unani Medicine (2008), PLIM, and Ghaziabad (UP).

- **Heavy Metal Analysis**

The heavy metal analysis for Lead (Pb), Arsenic (As),

Mercury (Hg) and Cadmium (Cd) was done as per Quality Control Manual for Ayurvedic, Siddha and Unani Medicine (2008), PLIM, Ghaziabad (UP) which was carried out by Shree Krishna Analytical Services, New Delhi.

- **Stability Study**

The stability/shelf life study of UMVT was carried out at the room temperature by visually examination for shape, color, odor and weight variation at the interval of 24 hours which was continued up to 6 months.

3. Results and Discussion

It is interesting to note that in spite of the popular Unani drug dosage forms (UDDFs), namely *hub* (pill) and *qurs* (tablet) etc. designed and developed exclusively for the oral route, a separate class of UDDFs had exclusively been developed for gynaecological disorders/diseases, such as *hamool*, *firzaja*, *marham*, *roghan*, *natool* etc. administered through vaginal route (*maslak-e-mahbil*). This exclusive route of drug delivery was first explored and employed by the Unani physicians. These formulations have found various disadvantages. Thus, there is a felt-need to design and develop a new dosage form to overcome disadvantages of existing Unani dosage form.

A Unani Mucoadhesive Vaginal Tablet (UMVT) was designed with the ingredients mentioned in the Unani classical literature. In this study, a number of procedures and tests were executed in order to design and develop UMVT.

3.1 Organoleptic Characteristics

The organoleptic characteristics of UMVT are as follows:

Table 1: Organoleptic Characteristics of UMVT

S. No.	Organoleptic Character	Observation
1.	Appearance	Tablet
2.	Color	Dark-Brown with white dots
3.	Smell	Agreeable
4.	Shape	Oval

3.2 Thickness / Diameter

The mean value of Thickness / Diameter was found 0.623 ±0.020.

3.3 friability

The mean value of Friability was found 0.0026 ± 0.00040.

3.4 pH at 1% & 10%

The mean value of pH at 1% and 10% were found 6.67± 0.11 and 6.90 ± 0.10, respectively.

3.5 Hardness

The mean value of hardness was found 2.40 ± 0.36.

3.6 Disintegration Time

The mean of Disintegration time was found 0.027 ± 0.006.

3.7 Swelling Index

The mean of Swelling Index was found 0.654 ± 0.011.

3.8 Weight Variation

The mean value of weight variation of UMVT was found 1.107 and ranges between 0.553 and 1.16.

3.9 Dissolution Time

The mean value of the dissolution profile (Cumulative drug release) of the prepared UMVT was found 87.83 ± 0.650.

Table 2: Cumulative drug release of UMVT

S No	Time (minuts)	Absorbance	Concentration (µg/ml)	Cumulative drug release (%)
1.	30	0.147	127.8	14.2
2.	60	0.350	331.2	36.8
3.	120	0.725	706.5	78.5
4.	240	0.739	720.9	80.1
5.	480	0.842	823.5	91.5

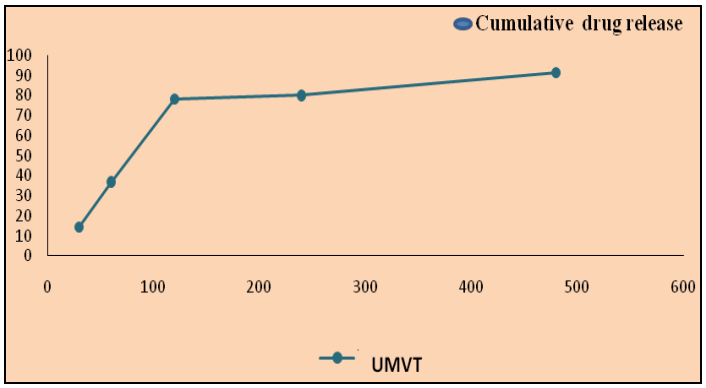

Fig 1: Cumulative drug release of UMVT

3.10 In *Vitro* Mucoadhesive Study

The *in vitro* mucoadhesive study of the UMVT was done and it was found that the tablet was not detached and it revealed strong mucoadhesive affinity.

The *in vitro* mucoadhesive study of UMVT was showed highest height of movement, i.e., showing highest mucin binding efficiency, and the slide bearing this tablet version was not detached at the highest level of inclination, i.e., 90 degree. It was observed that the UMVT having any strong mucoadhesive excipients which was responsible for strong binding with mucin protein.

3.11 Microbial Load

The microbial load of the UMVT is shown in the following table:

Table 3: Microbial load of UMVT

S No.	Test	Result
1.	Total Bacterial Count	2980 micro-organism/gram (NMT 100000 micro-organism/gram)
2.	Total Fungal Count	Absent/gram
3.	E. coli	Absent/gram
4.	Salmonella	Absent/gram
5.	S. aureus	Absent/gram
6.	Pseudomonas	Absent/gram

3.12 Heavy Metal Analysis

The findings of heavy metal analysis of the UMVT for the presence of Lead (Pb), Arsenic (As), Mercury (Hg) and Cadmium (Cd) are shown in the following table.

Table No: 4 Heavy Metal Analysis of UMVT

S. No.	Name of Heavy Metal	Result
1.	Lead	Less than 10 ppm
2.	Arsenic	Less than 3 ppm
3.	Mercury	Less than 1 ppm
4.	Cadmium	Less than 0.3 ppm

3.13 Stability/Shelf Life Study

The stability study of version-9.0 was done at room temperature for the duration of six (6) months, and formulation was finally evaluated for shape, color, odor and weight variation as shown in the table below:

Table 5: Stability of UMVT

S.No.	Duration (Weeks)	Parameter			
		Shape	Colour	Odour	Weight variation Test
1.	0 Week	Oval	Dark-Brown with white dots	Agreeable	Passed
2.	1 Weeks	Oval	Dark-Brown with white dots	Agreeable	Passed
3.	2 Weeks	Oval	Dark-Brown with white dots	Agreeable	Passed
4.	4 Weeks	Oval	Dark-Brown with white dots	Agreeable	Passed
5.	12 Weeks	Oval	Dark-Brown with white dots	Agreeable	Passed
6.	24 Weeks	Oval	Dark-Brown with white dots	Agreeable	Passed

4. Conclusion

Keeping in view of the current Unani pharmaceutical scenario, it is need of the hour to envisage a research study on design and development of Unani dosage forms. Accordingly, the study was based on design and development of a Unani Mucoadhesive Vaginal tablet in a novel dosage form for a very common gynaecological disorder, i.e. *waram-e-rahem*. Beginning with the preparation of standard operating procedures for UMVT, various physic-chemical parameters were conducted. Characterization of the UMVT: it was dark brown colour with white dots observed. It passed the weight variation parameter. The mean thickness was 0.623 ±0.020. The mean friability was 0.0026 ± 0.00040. Its mean pH 1% and pH 10% were 6.67± 0.11 and 6.90 ± 0.10, respectively. The mean hardness was 2.40 ± 0.36kg/cm^2.The mean disintegration time was 0.027 ± 0.006 and dissolution time (Cumulative drug release) was 87.83 ± 0.650.The highest SI was found with this version having HPMC and chitosan, natural polymers with good bio-adhesive nature. The tablet showed the highest mucin binding efficiency. For UMVT this parameter is an important otherwise the formulation will washed out easily from the vaginal area of administration.

Thus, this UMVT full filled this criteria and suitable for the specific site of application. The total bacterial count was found to be 2980 micro-organisms per gram (NMT 100000 micro-organisms per gram). The total fungal count was found absent per gram. As regard to *E.coli*, *Salmonella*, *S.aureus* and *Pseudomonas* were absent. Lead (pb), Arsenic (As), Mercury (Hg) and Cadmium (Cd) were found in the UMVT, less than permissible limit as per WHO guidelines. The test versions of UMVT were found to be stable during 6-month of storage period. On the basis of this study, the test formulation of UMVT was designed and developed successfully, but further clinical study is warranted to ensure its clinically efficacy *vis-a-vis* efficacy of classical dosage form so as to generate pharmaceutical evidence.

5. Conflict Of Interest

There is no conflict of interest.

6. Acknowledgement

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