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FORMULATION OF VAGINAL CREAM CONTAINING EXTRACTS OF LINUM USITATISSIMUM, FOENICULUM VULGARE, AND SALVIA OFFICINALIS FOR THE TREATMENT OF ATROPHIC VAGINITIS IN POSTMENOPAUSAL

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Abstract

Introduction: *Postmenopausal women with atrophic vaginitis had thinner epithelium, a lower vaginal maturation index, and higher vaginal pH. We chose phytoestrogens as an alternate treatment for atrophic vaginitis because of the potentially substantial side effects of long-term hormone replacement therapy use documented in a large prospective trial.*

Materials and methods: *In this research, Flax Seed, Foeniculum Vulgare, and Salvia officinalis were chosen as plants containing phytoestrogen. Three vaginal cream formulations (F1-F3) were prepared in this study. The physicochemical properties and stability of a vaginal lotion containing well-known phytoestrogen plants are investigated. This study evaluates Linum usitatissimum, Foeniculum vulgare seeds, and Salvia officinalis extract. Physical examination, stability, continuity, active ingredient release, and challenge test were the four key criteria for product evaluation.*

Results: *The release test revealed that extracts from formulation 2 and formulation 3 were slower to release than formulation1. It is owing to F1's decreased viscosity and F2 and F3's higher hydrophilic properties. The polyethylene glycol in formulations F2 and F3 may increase the hydrophilicity of the formulation, resulting in a stronger inclination of hydrophilic flavonoid extracts to the base and a decrease in extract liberation from the formulation. The w/o nature of the formulations allows them to lubricate or moisturize the vaginal epithelium, reducing Atrophic vaginitis symptoms.*

Conclusion: *Formulation 1 may be a viable alternative to the current treatments for atrophic vaginitis. To determine the efficacy of this herbal vaginal cream in treating the symptoms of atrophic vaginitis, however, additional scientific studies are necessary.*

Keywords: *postmenopausal, atrophic vaginitis, vaginal cream, flax, foeniculum, salvia officinalis.*

Introduction

Atrophic vaginitis (vaginal atrophy) is one of the consequences of menopause that is associated with decreasing vaginal epithelium thickness, vaginal pH, and drying vaginal walls. These happen because of reduced estrogen levels related to menopause and aging. [*Society NAM,*

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2013; Mahboubi M, 2019]. Also, because both vaginal and urinary are engaged, this condition is called genitourinary syndrome of menopause [*Nachtigall L et al., 2005*]. According to the North American Menopause Society, 10% to 40% of postmenopausal women suffer with Atrophic vaginitis, yet only 25% seek medical attention for the issue [*Society NAM 2007*]. Atrophic vaginitis may also develop in premenopausal women; this condition can be induced by surgical removal of the ovaries, chemotherapy, radiation, and adverse effects of antiestrogen medicines such as tamoxifen, danazol, leuprolide, and nafarelin [*Kaunitz A, 2001*].

Treatment mainly focuses on alleviation of symptoms and reduction vaginal alterations, which management include hormonal and non-hormonal therapies. Among the first-line therapies are non-hormonal remedies, lubricants, and moisturizers. The most common hormonal treatment for relieving symptoms is estrogen therapy. Systemic and local estrogen therapy is the typical route of delivery [*Society NAM, 2013*]. However, estrogen therapy is a rational approach to alleviate the bothering symptoms of Atrophic vaginitis; it may be unacceptable for some reason. The estrogen therapy is contraindicated in some postmenopausal women because of a history of cancer or risk of thromboembolism [*Suckling J et al., 2006*].

Vaginal estrogen affects fundamental physiology in a variety of ways, including increased blood flow, enhanced epithelium thickness, decreased PH, and increased secretions [*Pickar J, 2013*]. Chemical medicines are often used for atrophic vaginitis. Hormonal medications available in the market include Dienestrol (Ortho-Dienestrol Cream), Estradiol vaginal cream (Estrace), Estradiol (Vagifem), Conjugated estrogens (Premarin Vaginal Cream), Estradiol (Estring) [*Kaunitz A, 2001*]. Atrophic vaginitis has a negative effect of more than 50% on the quality of life in postmenopausal women [*Sinha A, Ewies A, 2013; Kargozar R et al., 2017*].

Concerns about the risk of increased estrogen hormone therapy are due to the use of non-steroidal estrogen mimetic. Phytoestrogens also increase the risk of breast cancer and endometrial hyperplasia [*Bedell S et al., 2014*]. Among the herbs that contain phytoestrogens, flax seeds, fennel, and sage were selected to prepare vaginal cream formulations of these plants. We chose phytoestrogens as an alternate treatment for atrophic vaginitis because of the potentially substantial side effects of long-term hormone replacement therapy usage documented in a large, prospective trial. This study evaluated the physicochemical properties and durability of a vaginal cream including Salvia officinalis extract, Linum usitatissimum, and Foeniculum Vulgare seeds.

Material and methods

Herbs: The Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences gave ethics approval (ajums.REC.1393.306). The goal of this study was to examine how effective flaxseed meals and flaxseed extract were at lowering climacteric symptoms in menopausal women.

Foeniculum vulgare has antibacterial, palliative, and anti-inflammatory properties in traditional medicine. Sage has traditionally been used to treat female infertility [*Khazaei M et al., 2011*]. Fennel seed is high in natural antioxidants that have antibacterial properties against gram-positive bacteria. Gallic acid, caffeic acid, ellagic acid, flavonol quercetin, and kaempferol are polyphenolic chemicals found in a methanol extract of fennel seeds [*Dua A et al., 2013*]. Fennel has a phytoestrogen activity because of the similarity between the chemical structure of lignans and steroid hormones [*Tham D et al., 1998*].

Extraction: Cold maceration was used to extract ethanol from flax seeds, fennel, and sage. The powdered plant (500 *g*) was macerated for three days at room temperature (25°C) in 1500 *ml* ethanol (80%, v/v). The results of the extract were then filtered, freeze-dried (FDCF-12012, Korea), and stored in the fridge.

The base composition included stearic acid, spermaceti, glycerin, and water. The oil phase, which included stearic acid and spermaceti, was combined and melted at 70°C. The aqueous phase was heated to the same temperature as the glycerin and water mixture. In the oil phase and the water phase, the preservatives were propylparaben and methylparaben, respectively. The oily phase was mixed with the watery phase, which was constantly stirred until it was cold. During mixing, the needed amounts (13%) of herbal extracts were added while the mixture was constantly stirred. Various substances were used to create different formulas (F1-F3) (Table).

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Table

Amounts of ingredients (%)

Variables	Components (%)	F1	F 2	F 3
Flaxseeds	8.3%	√	√	√
Sage	16%	√	√	√
Fennel	4%	√	√	√
Water	60%	√	√	√
Tween80	3.33%	√	√	√
Spermaceti	6.66%	√	√	√
Methyl Paraben	0.2%	√	√	√
Glycerin	0.075%	NA	NA	√
PEG 4000	0.15%	NA	√	√
PEG 6000	0.075%	NA	√	√
Stearic acid	20%	√	√	√

Tests: Products assessments were divided into four main categories:

A. Physical examination includes a review of homogeneity test, creaming, and coalescence
B. The stability and continuity of quality tests including thermal cycle and thermal variation, centrifugation, Freeze-thaw test, determination of pH, viscosity determination,
C. Evaluation of active ingredient's release from creams.
D. Microbial challenge test.

A. Physical examination

Microscopic samples of each formulation were obtained by spreading 0.5*g* of each formulation on a slide to assess homogeneity. Then, using an Olympus optical microscope, the decreases were observed [*Aulton M, 2001*].

The physical stability of each formulation was tested by sampling it and keeping it at room temperature for three months. After one week, one month, and three months of storage, their physical strength was assessed.

The samples were stored at 5°C for 48 hours (*h*) before being transferred to 25°C for another 48 *hours* (*h*) (*h*). After six repetitions of the procedure, the physical stability and appearance of the samples were evaluated. To evaluate thermal changes, three sets of 20 *g* samples of each formulation were stored at four, twenty-five, and fifty degrees Celsius. After 24 hours, one month, and three months, samples were evaluated for appearance and physical stability [*Poucher W, 1991*].

With 10*g* of each formulation inserted in a 1 cm diameter centrifuge tube, centrifugation tests were performed at 25°C and 2000 *rpm* for 5, 15, 30, and 60 minutes at 2000 *rpm*. After that, phase separation and solid sedimentation were evaluated in the samples [*Poucher WA, 1991*]. A 20 *g* sample of each formulation was stored at 45-50°C and 4°C for 48 hours each time to test physical stability. The operation was performed six times [*Poucher W, 1991*]. Measurements were taken 48 hours, one week, one month, and three months after each sample was created by dispersing 5*g* of the formulation in 95 *ml* of water, and measurements were performed 48 hours, one week, one month, and three months thereafter [*Poucher W, 1991*].

A Brookfield viscometer was used to assess the samples' rheological behavior (model DV-I with No. 6 spindle). The spindle velocity was gradually increased to the maximum, with each sample deposited in its own container. At 0.3, 0.6, 3, 6, and 60 revolutions per minute, the viscosity was measured.

C. Evaluation of the release of active ingredients from creams

The cellulose micro membrane was employed as a diffusion membrane in the release investigation, which was carried out in Franz diffusion cells. The membrane was placed between the chambers after being soaked in distilled water for 24 hours. Double distilled water was used to fill the receptor chamber and kept at a constant 37°C temperature. On the membrane, 0.5 *g* of each formulation were put.

To maintain sink condition, 2 ml samples were taken from the receptor phase and refilled with distilled water at suitable time intervals. Using the aluminum chloride colorimetric technique, the number of total flavonoids was measured. 1.5 *mL* of 95% ethanol, 0.1 *mL* of 10% aluminum chloride, 0.1 *mL* of 1M potassium acetate, and 2.8 *Ml* of distilled water were mixed with 0.5 *mL* of each sample. After 30 minutes of room temperature incubation, the absorbance of each combination was measured at 415*nm* with a Biochrom spectrophotometer (Bio wave II). A quercetin calibration curve was used to calculate the quantity at concentrations ranging from 3.125 to 100 *g/ml* [*Chang C et al., 2002*].

To evaluate the efficacy of the preservative in the formulation, a single microbiological challenge test was performed in accordance with USP30 for non-sterile products. Staphylococcus

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aureus (PTCC No. 1189), Pseudomonas aeruginosa (PTCC No. 1599), and Candida albicans (PTCC No. 5027) were added to a 20 *ml* pre-diluted sample of the formulation in sterile containers at 108 *cfu/ml*. Containers were kept at 22.52.5°C for bacteria and 37°C for candida for 28 days. According to the USP protocol, 1 *ml* of each incubated sample was poured onto a plate at appropriate time intervals using the pour plate count method (1, 7, 14, 21, and 28 days).The viable colony-forming units (cfu) were counted after a 48-hour incubation period. At the periods specified above, the quantity of cfu in each plate and variations in microbial populations were recorded.

Statistical methods: SPSS software version 22 was used for data analysis. The mean of quantitative data and the frequency of qualitative data were calculated. The mean of quantitative variables between the groups was compared by the T-test and the Mann-Whitney U or Kruskal–Wallis tests. The reliability coefficient was 95%, and statistically significant was $p<0.05$.

Results

A. Physical examination: All three formulations had a good appearance. Lamella for microscopic observation was taken for three formulations to see the physical appearance and no space between the particles and was devoid of nebulosity. After one week, one month, and three months of making the formulations, all three have no clots.

B. Sustainability and Quality Control: The quality of samples at 4-6, 25, and 45 to 50°C during 24*hr*, one and three months, was unchanged. The results of the thermal cycle test repeated six times show that there is no change in the quality of the formulations. After placing formulations for 5, 15, 30, 60 min and centrifuged at a speed 2000 *rpm*, no fracture or phase separation was observed in them.

Changes in the quality of all three formulations after successive heating and cooling at temperatures 40 to 50°C and 4°C at intervals of 48 *h* were not observed. The formulations had a pH of 4.6 to 5, which was similar to the pH of the vaginal fluid. It's because F1 has a lower viscosity (5770.333 ±68.579) while F2 and F3 have a higher hydrophilic nature (respectively 7253.333 ±513.246 and 7049.667 ±63579).

D. Releasing: Results from the release of 3 formulations and release of quercetin from each base cream are summarized in figure.

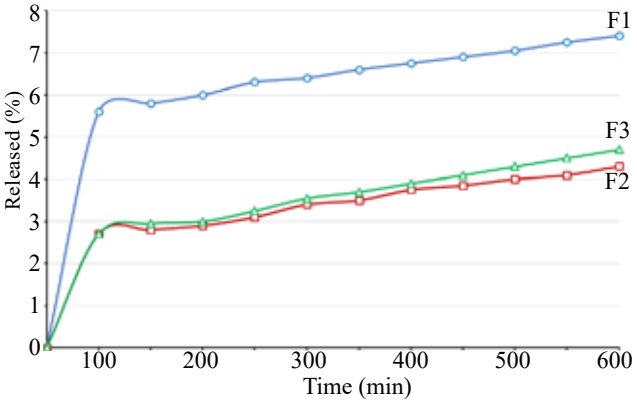

Figure. *Release behavior of selected* formulations *(F1, F2, and F3)*

E. Microbial challenge test: According to the results of the microbiological challenge, no growth was seen after one week and up to day 28. Within the first week, the quantity of candida Albicans fungus decreased, and after four weeks of storage, there was no rise in population. As a result, it was demonstrated that the formulations met the USP standards for antimicrobial preservation.

Discussion

Atrophic vaginitis symptoms affect the quality of life. Women don't intend to use several effective treatments, such as estrogen therapy, for thromboembolism risk, breast and endometrial malignancies, as well as various contraindications. One of the alternative treatments is phytoestrogens. In a survey conducted by Nachtigall et al. (2011), lignans, the Effect of lignans in reducing hot flashes was examined. In this study, 12 postmenopausal women with mild to moderate menopausal symptoms used a product made of flax seeds two times a day. This study shows that consumption of these products for 12 days significantly reduces symptoms of menopause include itching, bleeding, and vaginal dryness [*Nachtigall M et al., 2011*]. Ninety menopausal women were randomly assigned to one of three research groups: Group 1 received 100 *mg* of flaxseed extract each day. The second group was given 90 *g* of flaxseed per day, whereas Group III was given 1 *g* of Collagen per day (placebo group). The Kupperman index categorizes menopausal symptoms into three phases, beginning, end, and six months after treatment. They also examined endometrial and vaginal cytology. Both flaxseed extract and flax seed powder were effective compared with placebo in reducing the symptoms of menopause [*Colli M et al., 2012*]. Herbal medicinal products are used in replacement therapy for hot flashes associated with menopause. In

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a clinical study conducted by *Rahte S et al. (2013)*, the sage extract reduced the frequency and severity of hot flashes [*DerMarderosian A, 1999*].

In this research, *Flax Seed, Foeniculum Vulgare,* and *Salvia officinalis* were chosen as plants containing phytoestrogen. Three vaginal cream formulations (F1-F3) were prepared in this study. All formulations were homogenous and stable without creaming or coalescence during physical stability tests (centrifugation, thermal cycle, thermal variation, and freeze-thaw) and after three months of storage. The pH of the formulations was within the typical vaginal pH range and remained unchanged in this period. It is believed that the pH of the formulation may help regulate increased vaginal pH in Atrophic vaginitis. The stability of pH and other physical characteristics of creams indicates the compatibility of the extracts with different ingredients and no existence of chemical changes in the formulations. The microbial challenge test result also showed the suitability of preservatives used in the formulations.

An experiment was conducted by Bommer et al. (2011) to evaluate the effectiveness and preparation of Foeniculum Vulgare in the treatment of hot flashes and other menopausal complaints. However, clinical studies to prove the use of Foeniculum Vulgare in menopause have not been performed before. The results of this study, which controlled women with mild, moderate, and severe hot flashes for 12 months, show that the rate of hot flashes in the first eight weeks in these three groups decreased by 46%, 62%, and 79%, respectively. At eight weeks, the flushing of the three groups was 100% reduced. The treatment is well-tolerated, and the preparation of Foeniculum Vulgare has shown clinical value in treating hot flashes and menopausal symptoms [*Bommer S et al., 2011*]. Menopausal hot flashes are widely treated with herbal medical items as an alternative. In a clinical trial conducted in 2013, by *Rahte S et al. (2013)*, Foeniculum Vulgare tincture reduced the frequency and severity of hot flashes. The goal of this study was to figure out how Foeniculum Vulgare works to reduce hot flashes. The results of this study indicate that it is due to estrogenic flavonoids that this plant can be used as a safe and common herbal medicinal product during menopause [*Rahte S et al., 2013*]. Also, a clinical trial study with (5*g/day*) for eight weeks Foeniculum Vulgare positively affects vaginal atrophy in postmenopausal women [*Yaralizadeh M et al., 2016*]. However, a recent clinical trial on 60 postmenopausal women 100-*mg* soft capsules with 30% Foeniculum Vulgare was shown that this medication has not significantly improved vaginal atrophy [*Ghazanfarpour M et al., 2017*].

The penetrated quantity of total flavonoid, as measured by the Aluminum chloride colorimetric technique, was used to conduct the release research. The findings of the release test revealed that F2 and F3 extracts were slower than F1. It's because F1 has a lower viscosity while F2 and F3 have a higher hydrophilic nature. The presence of PEG in the F2 and F3 formulations may increase the formulation's hydrophilicity, resulting in a greater tendency for hydrophilic flavonoid extracts to bind to the base and less extract liberation. The w/o nature of the formulations, on the other hand, means that they have the capacity to lubricate or moisturize the vaginal epithelium, alleviating atrophic vaginitis symptoms.

Conclusion

Formulation 1 could be a suitable alternative to the current treatments for atrophic vaginitis. However, more clinical research is needed to confirm the efficacy of this herbal vaginal cream in treating the symptoms of atrophic vaginitis.

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