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Exploring the Safety and Compatibility of a Ready-to-Use Vaginal Film Vehicle for Drug Delivery: A Clinical Assessment

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Abstract

Purpose: This study aimed to evaluate the safety profile and clinical acceptance of FemPhyllo™, a novel ready-to-use base for mucoadhesive vaginal films, in the context of personalized medicine. The assessment focused on the vehicle's compatibility with vaginal mucosa and its influence on vaginal microbiota and pH levels. **Methods:** A non-comparative, controlled, clinical trial was conducted with healthy female subjects aged 18 to 50. The study involved a 4-week application of the vaginal film, with evaluations including clinical assessments, vaginal pH measurement, and microbiological cultures. Key exclusion criteria included recent infections, current medication use affecting mucosal integrity, and physiological conditions such as pregnancy. **Results:** The trial comprised 32 participants who completed the study, showing no significant adverse reactions related to the use of FemPhyllo™. Clinical observations confirmed the absence of discomfort, irritation, or other negative symptoms. Vaginal pH levels remained stable throughout the study period, with no significant alterations. Microbiological analysis showed no growth in pathogenic bacteria or fungi. **Conclusion:** FemPhyllo™ demonstrated a high level of safety and was well tolerated without disturbing the vaginal ecosystem. The stability of vaginal pH and the absence of microbial growth confirm its potential as a safe carrier for various pharmaceutical agents. Further studies are recommended to assess long-term impacts.

Keywords

Mucoadhesive Films, Gynecology, Vaginal Drug Delivery

1. Introduction

Women of reproductive age can be affected by different gynecological diseases

that can vary greatly in symptoms and severity, raising worldwide social and public health concerns. Common gynecological disorders include dysmenorrhea, endometriosis, vulvovaginal candidiasis, human papillomavirus (HPV) infection, polycystic ovary syndrome, and ovarian dysfunction [1] [2]. Treatment options will depend on the underlying condition and might include hormonal therapies (e.g., estradiol, gestrinone, progesterone, testosterone), non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., nimesulide, piroxicam), antifungals (e.g., clotrimazole, fluconazole, ketoconazole), antibiotics (e.g., clindamycin, metronidazole), among other active pharmaceutical ingredients (APIs) [3].

As most treatments are traditionally available through oral administration, they are usually associated with different adverse reactions, such as gastrointestinal upset (e.g., nausea, diarrhea), androgenic symptoms (e.g., breast discomfort, irritability), and other general effects (e.g., headaches, drowsiness, and dizziness). For this reason, developing patient-friendly non-oral routes is necessary to improve the delivery of certain medications and avoid first-pass metabolism effects [3]-[5].

The vaginal mucosa presents a compelling route for both local and systemic drug delivery, owing to its dense vascularization, extensive surface area, relatively neutral pH, and absence of first-pass hepatic metabolism. Despite these advantages, traditional vaginal dosage forms such as creams, gels, pessaries, and suppositories are associated with significant limitations, including short residence time, variable drug distribution, leakage, and messiness, all of which can negatively impact patient adherence and treatment efficacy. These formulations may also alter the vaginal microenvironment by increasing moisture or disrupting the local microbiota, leading to irritation, discomfort, or secondary infections. In contrast, vaginal films offer a novel and advantageous alternative [6]-[8].

Vaginal films present relevant advantages over other vaginal dosage forms since they are smaller, easy to store and transport, and have increased stability, especially compared to gels, creams, and suppositories. Their thin, polymeric structure allows for rapid dissolution or sustained release, depending on the formulation, while ensuring improved mucoadhesion and uniform drug distribution. Films are discreet, portable, easy to administer without an applicator, and reduce the likelihood of leakage or dose variability [9]. They can be easily folded and inserted by the patient. Collectively, these features position vaginal films as a promising alternative to overcome the drawbacks of conventional dosage forms, with the potential to enhance therapeutic outcomes, patient acceptability, and adherence [8] [10] [11].

From a pharmaceutical perspective, vaginal films can be compounded using a variety of ingredients that need to be combined to achieve adequate viscosity of the base (prior drying), mucoadhesiveness, and stability. Also, the base should not be irritant to the mucosa and must promote the proper release of the API. Given these factors, compounding pharmacies would benefit from ready-to-use bases that were previously validated, reducing operational and technical difficulties.

Therefore, the objectives of this study were to investigate the safety profile and

clinical acceptance of FemPhyllo™, a novel ready-to-use base for the production of mucoadhesive vaginal films in the context of personalized medicine. Its composition includes polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC), two widely used film-forming agents known for their excellent mucoadhesive properties, mechanical stability, and biocompatibility. Polysorbate 80 and PEG-400 serve as solubilizers and plasticizers, improving the flexibility and uniformity of the film while facilitating the incorporation and release of both hydrophilic and lipophilic active ingredients. Sodium polyacrylate, a superabsorbent polymer, enhances film hydration and contributes to prolonged residence time by forming a gel-like matrix upon contact with vaginal fluids. Disodium EDTA is included as a chelating agent to stabilize the formulation and enhance preservative efficacy. The antimicrobial agents sorbic acid and benzalkonium chloride ensure microbiological safety, while lactic acid helps maintain the acidic vaginal pH, supporting the natural microbiota and preventing overgrowth of pathogenic species [12]. All components are generally recognized as safe (GRAS) [13] and are commonly employed in pharmaceutical and personal care products, making FemPhyllo™ a reliable and well-tolerated platform for vaginal film development. Clinical assessment, vaginal pH, and microbiological tests were performed.

2. Materials and Methods

2.1. Study Design

The skin and genital mucosa acceptance of the investigational product was examined through a non-comparative, controlled clinical trial. Healthy female subjects aged 18 to 50 years with intact skin in the tested area were eligible for the study. Written informed consent was obtained from all participants. The exclusion criteria include pregnancy or breastfeeding; menstruation period during the study visits; amenorrhea or menstrual dysfunctions; sexual intercourse up to forty-eight hours before the start of the study; urogenital or vaginal infection in the last thirty days; current use of medications such as antibiotics, corticosteroids, immunosuppressants, or anti-histaminic.

2.2. Investigational Product

The investigational product FemPhyllo™ was provided by the sponsor (Fagron, Rotterdam, The Netherlands) and labeled with adequate codes and usage directions. The product samples were appropriately stored at a controlled temperature (20˚C - 25˚C) and restricted access environment. The product release was controlled by the principal investigator or by a previously designated technical staff.

2.3. Skin and Genital Mucous Acceptance Study

A total of 37 volunteers were screened, and out of these, 36 were eligible to participate. Four subjects withdrew from the study and were excluded. The reasons for declining participation were not related to the investigational product. The anal-

yses were based on 32 subjects who had completed the entire 4-week-long study (Figure 1).

The subjects were instructed not to apply any product to the tested areas and not to change any cosmetic habits (including personal hygiene) during the study period. In addition, participants should not have sexual intercourse within forty-eight hours before the study visits. Participants received detailed information about the product usage as follows:

- Fold the film in half and place it on the tip of the middle finger;
- In a comfortable or lying position, insert the film fully into the vaginal cavity, where it will immediately adhere to the mucous layer;
- Apply daily for 28 ± 2 days.

2.3.1. Clinical Assessment

Clinical assessment of the subjects was performed by a registered gynecologist on the initial visit (T0) and after 28 ± 2 days of product use (T28). Subjects were clinically assessed throughout the study to identify possible adverse reactions such as discomfort, irritation, and burning sensation and to identify correct product use. During the study period, subjects were instructed to contact the study coordinator at any time if any adverse reactions were observed.

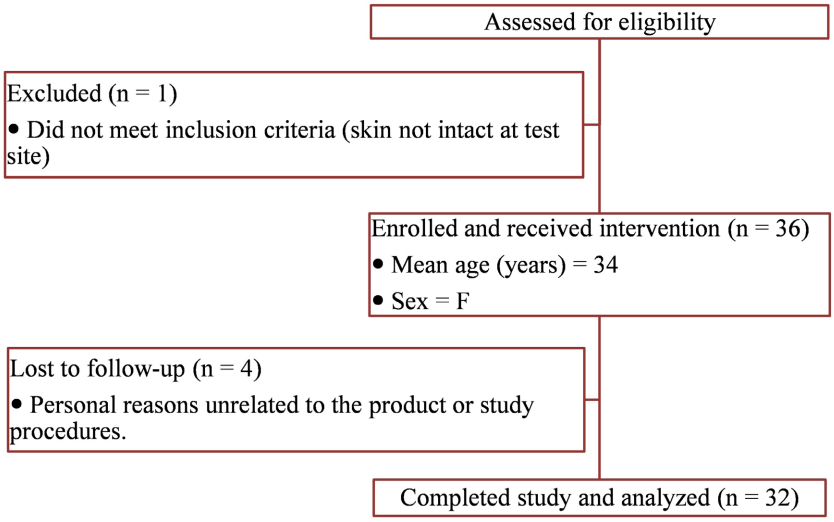

Figure 1. Flow diagram of participant inclusion, allocation, follow-up, and analysis. Of the 37 individuals assessed for eligibility, one participant was excluded for not meeting the inclusion criterion of having intact skin in the application area. Thirty-six participants were enrolled and received the investigational product. Four participants were lost to follow-up for personal reasons unrelated to the study. A total of 32 participants completed the study and were included in the final safety and efficacy analysis. All participants were female, aged 18 - 50 years (mean age 34). Caption: F (female).

2.3.2. Vaginal pH Assessment

The vaginal pH was evaluated at the beginning (T0) and at the end (T28) of the study. During the clinical assessment, indicator tapes were applied to the vaginal introitus, and the pH was measured.

2.3.3. Microbiological Assessment

Bacterioscopic collection and vaginal secretion culture were performed to quantify the microorganisms in the vaginal region at the beginning (T0) and at the end (T28) of the study.

The collection was carried out during the gynecological clinical assessments using a swab technique in the region of the vaginal introitus. The collected material was suspended in 5 mL of Lactobacillus MRS broth (deMan, Rogosa, and Sharpe) and kept refrigerated until the time of microbiological analysis. The collected samples were submitted to serial dilution using sterile water until a dilution of 10^{-5}.

To quantify *Escherichia coli*, 0.1 mL of the dilutions 10^{0}, 10^{-1}, and 10^{-2} were plated using the surface technique in EMB (Eosin Methylene Blue) Agar. The plates were incubated under aerobiosis conditions at 32.5 ± 2.5˚C for 72 hours. After incubation, the colonies present on the plates were counted.

To quantify *Candida albicans*, 1 mL of the dilutions 10^{-1}, 10^{-2}, and 10^{-3} were plated using the pour plate technique, and SDA (Sabouraud Dextrose Agar) was used. The plates were incubated under aerobic conditions at 22.5 ± 2.5˚C for 5 days. After incubation, the colonies present on the plates were counted.

2.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki Ethical Principles [14] and according to Good Clinical Practices (Document of the Americas and ICH E6: Good Clinical Practices) [15] [16].

3. Results

3.1. Clinical Assessment and Vaginal pH Assessment

During the study, subjects did not present adverse clinical signs in the genital mucosa related to product use. Additionally, no subjects reported product-related discomfort sensations or irritations. Therefore, the product showed good skin and mucosal acceptance under the study conditions. The study population consisted of healthy female participants aged 18 to 50 years (mean age: 34), representing a typical reproductive-age group. While no apparent correlation between age and tolerability outcomes was observed, the relatively narrow demographic range may limit generalizability to postmenopausal women or those with comorbid gynecological conditions.

No statistically significant change in the vaginal pH value was observed. The mean pH value at baseline (T0) was 4.9, and at the end of the study (T28) was 5.0.

3.2. Microbiological Assessment

3.2.1. *Escherichia coli*

Table 1 shows that compared to the log (logarithm) count of the microorganism at the baseline (T0), no statistically significant change was observed after the study endpoint (T28) (differences 0.03 (95% Confidence Interval (CI) −0.03; 0.09)).

Table 1. Descriptive statistics and results of the comparison between T0 and T28.

Statistic	T0	T28	Decimal reduction
Mean (log)	1.03	1.00	0.03
Standard error	0.03	0.00	0.03
IC 95%	[0.97; 1.09]	[1; 1]	[−0.03; 0.09]
% of variation (on the mean)			−2.9
% of subjects with a reduction			0.0
% of subjects with an increase			3.1
P-value			1.000*

*Significant at a 5% level (Wilcoxon Signed-Rank test) [17].

3.2.2. *Candida albicans*

Table 2 shows that compared to the log count of the microorganism at the baseline (T0), no statistically significant change was observed after the study endpoint (T28) (differences 0.12 (95% CI −0.27; 0.52)).

Table 2. Descriptive statistics and results of the comparison between T0 and T28.

Statistic	T0	T28	Decimal reduction
Mean (log)	1.75	1.63	0.12
Standard error	0.25	0.24	0.19
IC 95%	[1.24; 2.27]	[1.14; 2.12]	[−0.27; 0.52]
% of variation (on the mean)			−6.9
% of subjects with a reduction			21.9
% of subjects with an increase			12.5
P-value			0.351

*Significant at a 5% level (Wilcoxon Signed-Rank test) [17].

4. Discussion

This study aimed to evaluate the safety profile of vaginal films produced with the ready-to-use base, FemPhyllo™. Even though there are multiple studies regarding different APIs used in gynecological treatments, this is not the case for the different excipients and bases carrying out these treatments, which enhances the relevance of our investigation [18]. Understanding the influence of excipients in drug delivery systems is as relevant as the APIs themselves, as in many cases, they might be the responsible ingredients for adverse reactions. [19] In this controlled clinical trial, the investigational product did not induce adverse clinical signs in the vaginal mucosa or product-related discomfort sensations.

Vaginal films have gained a lot of attention in the last decade as an innovative dosage form for different APIs such as hormones, contraceptives, antifungals, antimicrobials, and antivirals [8] [20]. Previous studies indicated that vaginal films are preferred compared to other dosage forms due to their easy portability, appli-

cation, storage, and handling [8] [21] [22]. In addition, suppositories, gels, and creams have shown low retention time in the vaginal cavity, potentially compromising their therapeutic efficacy [23]. Results of chemical and microbiological stability studies suggested that the low water activity in film's formulation makes them less prone to microorganism overgrowth, which is a significant advantage compared to other available dosage forms [24]. Moreover, excessively hyperosmotic gels can potentially lead to irritation and inflammation of the skin and mucosa [21]. In line with prior literature, this study found no adverse clinical signs in the vaginal mucosa or discomfort sensations associated with the use of the product among the subjects.

Furthermore, the relationship between the human vaginal pH and microbiota has been an ongoing area of interest in understanding vaginal physiology, diseases, and drug development [25]. Studies have suggested that a healthy vaginal environment depends on the balance between normal vaginal flora, endocrine regulation, and mucosal epithelial barrier [26]. Also, this balance is a dynamic process that constantly changes throughout different stages of a woman's life [27]. Thus, subjects' vaginal pH value and microbiota were evaluated at baseline (T0) and at the end (T28) of the study. No statistically significant change in the vaginal pH value was observed. The healthy pH value of the human vaginal environment normally ranges from 3.8 to 5.0, which is slightly acidic [25] [28]. This value is influenced by the Lactobacilli population due to the production of lactic acid in the mucosa [4]. It has been previously proposed that unbalanced vaginal microbiota may affect pH values, increasing the possibility of bacterial overgrowth and the development of vaginitis [25]. The results of the current study showed no statistically significant change in *Escherichia coli* and *Candida albicans* count. This finding also suggests that the protective functions of the subject's vaginal microbiota were maintained.

Although the results of this study support the safety and tolerability of FemPhyllo™, several limitations should be acknowledged. First, the absence of a placebo or comparator group restricts the ability to differentiate between effects related to the investigational product and those related to natural variations in the vaginal environment. Second, the relatively short duration of the study (28 ± 2 days) limits the assessment of long-term impacts on the vaginal microbiota, mucosal integrity, and patient acceptability. Additionally, while the product demonstrated excellent short-term safety, extended exposure and repeated use may present different tolerability profiles that would benefit from further investigation. Future randomized controlled trials with extended follow-up periods are essential to confirm these findings and assess the product's performance in diverse patient populations and clinical scenarios.

5. Conclusion

During this study, according to the methodology applied to evaluate the safety of FemPhyllo™, the investigational product can be considered safe under the studied

conditions. FemPhyllo™ did not lead to adverse clinical signs in the skin and genital mucosa, changes in the vaginal pH value, or induce microorganism overgrowth.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Funding

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Conflicts of Interest

The authors are employees of Fagron B.V. The funder (Fagron B.V.) had no influence on the design of the study or on the collection and analysis of data. In addition, all authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Statement of Human and Animal Rights

The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and with the Good Clinical Practices (Document of the Americas and ICH E6). Informed consent was obtained from all subjects involved in the study.

Author Contributions

Data curation, B.M., H.P.; writing—original draft preparation, B.M.; writing—review and editing, H.P., C.S., S.K.; visualization, B.M., H.P.; supervision, H.P. All authors have read and agreed to the published version of the manuscript.

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