

## The Leakage Test: Evaluation of the Leakage Potential of PCCA Ellage™

**SUMMARY:** Vaginal drug delivery offers many advantages but conventional vaginal dosage forms have the potential to leak rapidly due to the vaginal fluid that is continuously released. The leakage test has shown that PCCA Ellage Anhydrous Vaginal, a mucoadhesive base designed specifically to optimize drug delivery in the vaginal mucosa, and PCCA formulas 13845 and 13834 have high retention potential *in vitro* – superior to the OTC long-lasting vaginal moisturizer.

### Introduction:

The vaginal mucosa offers a large surface area and rich blood supply, making it a promising site for delivery of medication in the treatment of several conditions (e.g., vaginitis, infections) and also in hormone replacement therapy. Vaginal drug delivery, however, faces a multitude of challenges; in particular, the leakage potential of drugs due to the vaginal fluid that is continuously released [1]. Conventional vaginal dosage forms such as creams, gels, and foams have a limited residence time (time at the site of action) and efforts are made to prolong the contact time between the medication and the mucosal tissue. Also, conventional dosage forms are commonly runny or messy, especially the vaginal gels [2]. PCCA Ellage Anhydrous Vaginal is a mucoadhesive base designed specifically to optimize drug delivery in the vaginal mucosa. Compounded medicines prepared with PCCA Ellage are likely to remain at the site of action for a longer period of time, without leakage or messiness, potentially improving patient acceptance and compliance.

The aim of this study was to test *in vitro* the leakage potential of PCCA Ellage, alone and with common active pharmaceutical ingredients, in comparison to an over-the-counter (OTC) vaginal moisturizer of reference that claims to be long-lasting (up to 3 days). Upon vaginal administration, gels and creams become diluted with vaginal fluids which may lead to changes in their rheological and mucoadhesive properties, with increased leakage and runny discomfort. In order to simulate *in vivo* conditions and account for any loss of beneficial physical properties, the leakage test was also performed on the corresponding diluted formulas for PCCA Ellage; Estriol 0.1% and Testosterone 0.1% in Ellage (PCCA formula 13845); Amitriptyline 2% and Baclofen 2% in Ellage (PCCA formula 13834); and the OTC long-lasting vaginal moisturizer.

### Methodology:

The leakage test was conducted at the PCCA R&D Lab in accordance to an adapted method of the *in vitro* leakage potential test by Andrade *et al.* [3]. Initially, a Vaginal Fluid Simulant (VFS) was prepared to model the fluid produced in the human vagina by healthy, nonpregnant premenopausal women. The composition of the fluid medium was based on the research by Owen and Katz and includes the following ingredients: NaCl 3.51 g, KOH 1.4 g, Ca(OH)<sub>2</sub> 0.222 g, BSA 0.018 g, lactic acid 2.0 g, acetic acid 1.0 g, glycerol 0.16 g, urea 0.4 g, glucose monohydrate 5.0 g, HCl qs pH 4.2-4.5 and H<sub>2</sub>O qs 1,000 mL [4].

A total of 4 test formulas were prepared, as follows: PCCA Ellage; Estriol 0.1% and Testosterone 0.1% in Ellage; Amitriptyline 2% and Baclofen 2% in Ellage; and the OTC long-lasting vaginal moisturizer. A diluted version of these formulas was also prepared by adding 2 mL of each formula to 0.75 mL of VFS. As a result, a total of 8 formulas (diluted and undiluted) were prepared for the leakage test.

An aliquot of 25 mL of agar solution – 1.5% of agarose (w/v) in VFS – was poured into a Petri dish (100 mm) and the resulting agar plate was placed at room temperature for solidifying. Each formula was tested in triplicate so this procedure was repeated for a total of 24 Petri dishes. Before the experiment, the agar plates were placed inside an incubator (VWR; model 2020) at 37°C, in a vertical position and at an angle of 60°.

Using a syringe, an aliquot of 0.5 mL of each test formula was deposited onto the top of the agar plate and the time taken for the test formulas to reach the bottom of the agar plate was recorded, up to a maximum of 5 minutes. The running distance of the test formulas was measured along the agar plate.

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### Results and Discussion:

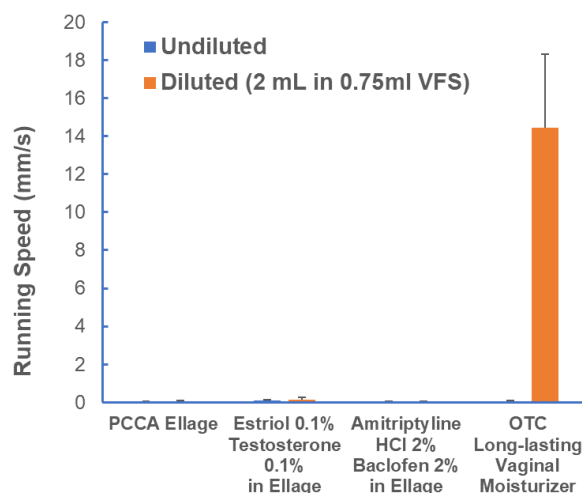
The 4 test formulas were divided in two groups: diluted and undiluted, with 12 agar plates in each group. There was no change for the undiluted test formulas as these remained on the top of the agar plates, where they were originally placed, throughout the study period of 5 minutes (Figure 1a, top). This fact demonstrates that PCCA Ellage, PCCA formulas 13845 and 13834, as well as the OTC long-lasting vaginal moisturizer, have high retention potential to the warm and moisturized surface containing VFS.

PCCA Ellage	Estriol 0.1% Testosterone 0.1% in Ellage	Amitriptyline 2% Baclofen 2% in Ellage	OTC Long- Lasting Vaginal Moisturizer
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**Figures 1a and 1b.** The leakage test (randomly selected agar plates) for PCCA Ellage, PCCA formulas 13845 and 13834, and the OTC long-lasting vaginal moisturizer: undiluted formulas (1a) and diluted formulas (1b).

When the test formulas were diluted with the VFS, to simulate *in vivo* conditions where vaginal dosage forms become diluted with vaginal fluids, it was observed that PCCA Ellage and the corresponding PCCA formulas still remained on the top of the agar plates (Figure 1b, bottom). The average running speed of these formulas on the agar plates was close to zero, as shown in Figure 2, which reinforces the unique high retention potential of PCCA Ellage. On the contrary, the OTC long-lasting vaginal moisturizer ran down the agar plate, travelling across 10 cm, and reached the bottom of the plate in less than 10 seconds (average running speed of 14.44 mm/s, Figure 2).



**Figure 2.** The leakage test: average running speed for PCCA Ellage, PCCA formulas 13845 and 13834, and the OTC long-lasting vaginal moisturizer (diluted and undiluted formulas).

### Conclusions:

The leakage test has shown that PCCA Ellage Anhydrous Vaginal, and its corresponding PCCA formulas, have high retention potential *in vitro* – superior to the OTC long-lasting vaginal moisturizer. As such, PCCA Ellage is expected to adhere *in vivo* to the vaginal mucosa for a long period of time, despite the regular secretions of vaginal fluid, without leakage or messiness.

### References:

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