Development of a mucoadhesive, anhydrous and self-emulsifying vaginal base for compounded medications

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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 and also in hormone replacement therapy. However, vaginal drug delivery faces multiple challenges; in particular, the leakage potential of drugs due to the vaginal fluid that is continuously released [1]. Conventional dosage forms such as creams, gels, and foams have limited contact time with the vaginal mucosa and are commonly runny or messy, especially the vaginal gels [2]. Vaginal compounded medications offer an alternative treatment option that is customized to meet the individual needs of each and every women. The purpose of our research was to develop a mucoadhesive, anhydrous and self-emulsifying base for the preparation of vaginal compounded medications. Mucoadhesive to increase the contact time between the medication and the vaginal mucosa, potentially improving patient acceptance and compliance. Self-emulsifying to create a spontaneous emulsion when it comes into contact with water from vaginal fluids. This emulsion then releases the active pharmaceutical ingredients (APIs) from the base to the vaginal mucosa. Once the APIs are released, the emulsifier system in the base also holds the drugs to the surface and increases the contact time. This novel and promising technology, named Self-Emulsifying Drug Delivery Systems (SEDDS), has the potential to maximize drug solubility and bioavailability.

Methodology: The mucoadhesive properties of the newly-developed vaginal base were evaluated by the ex vivo testing on animal vaginal tissues and the bioadhesion testing using a texture analyzer. In addition, the leakage potential was evaluated in accordance to an adapted method of the in vitro leakage potential test. The self-emulsifying properties were tested by microscopic evaluation and also by fluorescence microscopy.
A Vaginal Fluid Simulant (VFS) was prepared to model the fluid produced in the human vagina by healthy, nonpregnant premenopausal women [3] and it was used in all tests described above.

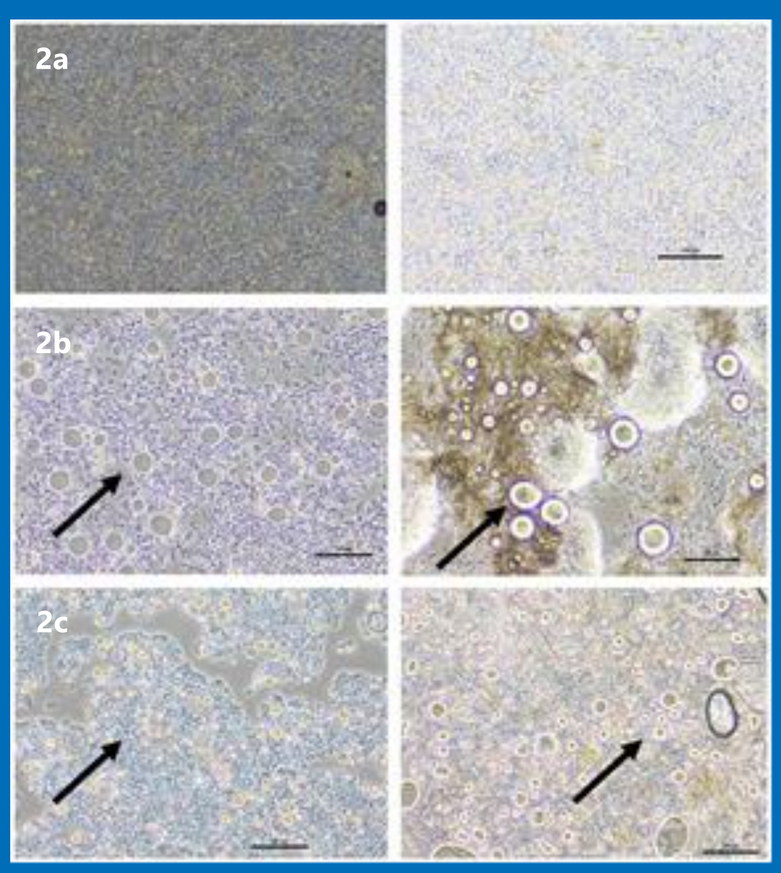
Figures 1a-1b. The leakage test for the vaginal base and corresponding 2 formulas versus the OTC long-lasting vaginal moisturizer (from left to right): undiluted formulas (1a) and diluted formulas with VFS (1b).

The self-emulsifying properties of the newly developed vaginal base were explored further by evaluating the distribution pattern of substances with different solubilities, namely fluorescein sodium (hydrophilic substance) and curcumin (lipophilic substance). The fluorescence microscopy examination (green fluorescent light) demonstrated that when the anhydrous vaginal base was mixed with the VFS at 37°C, the hydrophilic and lipophilic substances displayed opposite behaviors within the vaginal base, as shown in Figures 3a-3b (examples highlighted with arrows). As expected, the insoluble curcumin was encapsulated inside the dispersed lipophilic droplets, whereas the soluble fluorescein sodium remained in the continuous aqueous phase (outside the droplets).

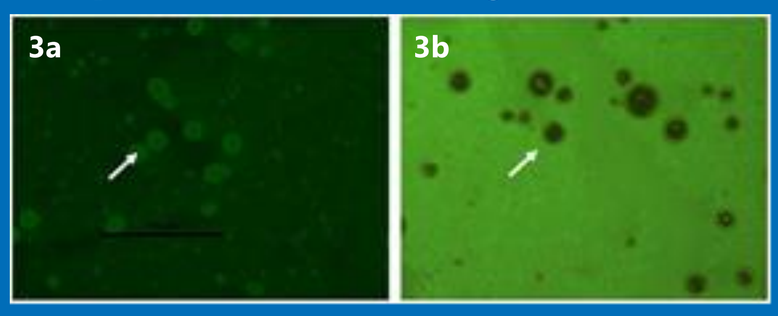
Results: An innovative proprietary base (Ellage Anhydrous Vaginal) was developed specifically for vaginal drug delivery. This is the first mucoadhesive, anhydrous and self-emulsifying base with applications in pharmaceutical compounding [4].

Mucoadhesive Properties
The mucoadhesion of the vaginal base was tested and compared to an over-the-counter (OTC) vaginal moisturizer of reference that claims to be long-lasting (up to 3 days).
The testing on the frozen pig vaginal tract demonstrated that the fluorescently labelled vaginal base was superior to the OTC and remained on top of the ex vivo tissues despite the intermittent rinsing in VFS at 12 pre-determined time-points. The bioadhesion testing showed that the vaginal base and the OTC required similar average work of adhesion by the CTX Texture Analyzer equipped with a load cell of 1.5 Kg, and it was significantly higher than the VFS alone (negative control). The leakage test was performed on 4 products: vaginal base, estriol 0.1% and testosterone 0.1% in vaginal base; amitriptyline 2% and baclofen 2% in vaginal base; and the OTC. It was observed that all products remained on the top of the agar plates with the exception of the OTC diluted with VFS (Figures 1a-1b).

Self-Emulsifying Properties
Under the microscope (100x), it was observed that the original vaginal base does not have any droplets (Figure 2a). However, upon mixture with VFS in a 1:1 ratio, the development of droplets was observed and these droplets decreased in size from 1 min to 5 min of incubation at 37°C (Figures 2b and 2c). This process took place also when the APIs amitriptyline 2% and baclofen 2% were incorporated into the anhydrous vaginal base (Figure 2, right column). This phenomenon is the process of self-emulsification which is a unique property of the vaginal base.



Figures 2a-2c. Microscopic evaluation of droplet size formation (100x) for the vaginal base, with and without APIs (selected droplets highlighted with arrows): original (2a), 1:1 in VFS t=1min (2b) and 1:1 in VFS t=5min (2c).



Figures 3a-3b. Fluorescence microscopy (green fluorescent light) for curcumin 1% (3a) and fluorescein sodium 0.02% (3b) in the vaginal base with VFS. Arrows highlight the interior of selected droplets for curcumin and the exterior of selected droplets for the fluorescein sodium, where the lipophilic and hydrophilic substances are located.

Conclusions: A mucoadhesive, anhydrous and self-emulsifying vaginal base was recently developed for the preparation of compounded medications. The tests performed to evaluate the mucoadhesive properties have demonstrated that the vaginal base has high retention potential in vitro – superior to the long-lasting vaginal moisturizer of reference. As such, the vaginal base and its corresponding compounded medications are 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. Furthermore, it was demonstrated that the anhydrous vaginal base exhibits its self-emulsifying properties in the presence of variable amounts of vaginal fluid simulant. This is a key property of the vaginal base taking into account the vaginal fluids in women, which vary upon the menstrual cycle and in the presence of conditions such as vaginal dryness. In clinical practice, lipophilic APIs are expected to exhibit a slow drug release from the vaginal base due to the encapsulation in the lipophilic droplets, whereas hydrophilic APIs are expected to exhibit a fast drug release directly from the aqueous phase.

References: 1. Pereira, R. and Bruschi, M. Vaginal mucoadhesive drug delivery systems. *Drug Development and Industrial Pharmacy*, 38 (6), 643-52 (2012). 2. Hardy, E.; Jiménez, A.L.; de Pádua, K.S. and Zaneveld, L.J. Women's preferences for vaginal antimicrobial contraceptives. III. Choice of a formulation, applicator, and packaging. *Contraception*, 58 (4), 245-9 (1998). 3. Owen, D.H. and Katz, D.F. A vaginal fluid simulant. *Contraception*, 59 (2), 91-5 (1999). 4. PCCA. Ellage Anhydrous Vaginal. Available at: https://www.pccarx.com/Products/ProductCatalog?pid=30-5110 (Accessed: January 31, 2021).