Evaluation of the Self-Emulsifying Properties of PCCA Ellage™ *Part 2: Fluorescence Microscopy*

SUMMARY: The distribution pattern of lipophilic and hydrophilic substances in PCCA Ellage, with and without VFS, was evaluated by fluorescence microscopy (white and green fluorescent lights). Curcumin 1% (lipophilic) and fluorescein sodium 0.02% (hydrophilic) distributed evenly in PCCA Ellage alone but exhibited opposite behaviors when PCCA Ellage was gently mixed with VFS.

Introduction & Methodology:

PCCA Ellage Anhydrous Vaginal (Figure 1) is an innovative proprietary base with self-emulsifying properties that creates a spontaneous emulsion when it comes in contact with water from vaginal fluids. This emulsion releases the active ingredients from the base to the mucosa. Once the active ingredients 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 [1]. The purpose of this study is to explore further the self-emulsifying properties of PCCA Ellage by evaluating the distribution pattern of substances with different solubilities. A fluorescence microscopy test was performed at PCCA R&D using hydrophilic and lipophilic substances incorporated in PCCA Ellage. Fluorescein sodium (Sigma-Aldrich, #F6377) was the hydrophilic substance used (1 mg/mL water solubility) whereas curcumin (PCCA #C30-3497) was the lipophilic substance used (insoluble in water) [2]. These substances were selected for their fluorescence properties and represent both hydrophilic and lipophilic active pharmaceutical ingredients (APIs) that will be used in clinical practice.

Figure 1. *Photograph of PCCA Ellage 500 g container with TopiClick and applicator.*

The test formulations were prepared by adding fluorescein sodium 0.02%, or curcumin 1%, with glycerin 5% to PCCA Ellage. The formulations were mixed using the EMP at a setting of 5 for 2 min. A sample from each was saved for fluorescence microscopy. The test formulations were then gently mixed with a Vaginal Fluid Simulant (VFS) – 1:2 ratio (w/v) – at 37°C. Within 5 min from extemporaneous preparation, samples from both test formulations, with and without VFS, were observed under the microscope with white light and also green fluorescent light. Photographs were taken using a Nikon Eclipse TS100 inverted phase microscope coupled with the NIS-Elements imaging software.

Results & Discussion:

The hydrophilic and lipophilic substances distributed evenly in PCCA Ellage when mixed for 2 min in the EMP, as shown by the homogeneous fluorescence under green fluorescent light (Figure 2). Upon mixing with VFS at 37°C, PCCA Ellage exhibited its unique self-emulsifying properties by creating an emulsion, i.e., dispersed lipophilic droplets in an aqueous continuous phase. As expected, the hydrophilic and lipophilic substances displayed opposite behaviors within the self-emulsifying cream, as shown in Figure 3. The insoluble curcumin was encapsulated inside the droplets whereas the soluble fluorescein sodium remained in the aqueous phase, outside the droplets (examples highlighted with arrows for both white and green fluorescent lights). In clinical practice, lipophilic APIs are thus expected to exhibit a slow drug release from the PCCA Ellage Anhydrous Vaginal due to the encapsulation whereas hydrophilic APIs are expected to exhibit a fast drug release.

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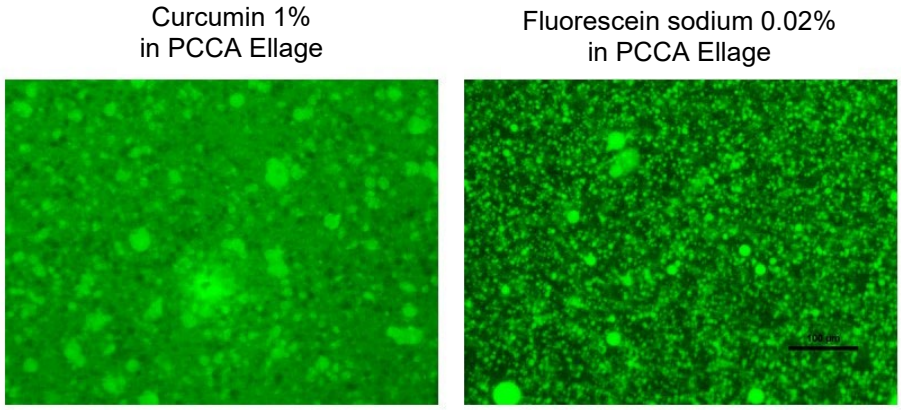

Figure 2. *Fluorescence microscopy (green fluorescent light) for curcumin 1% and fluorescein sodium 0.02% in PCCA Ellage.*

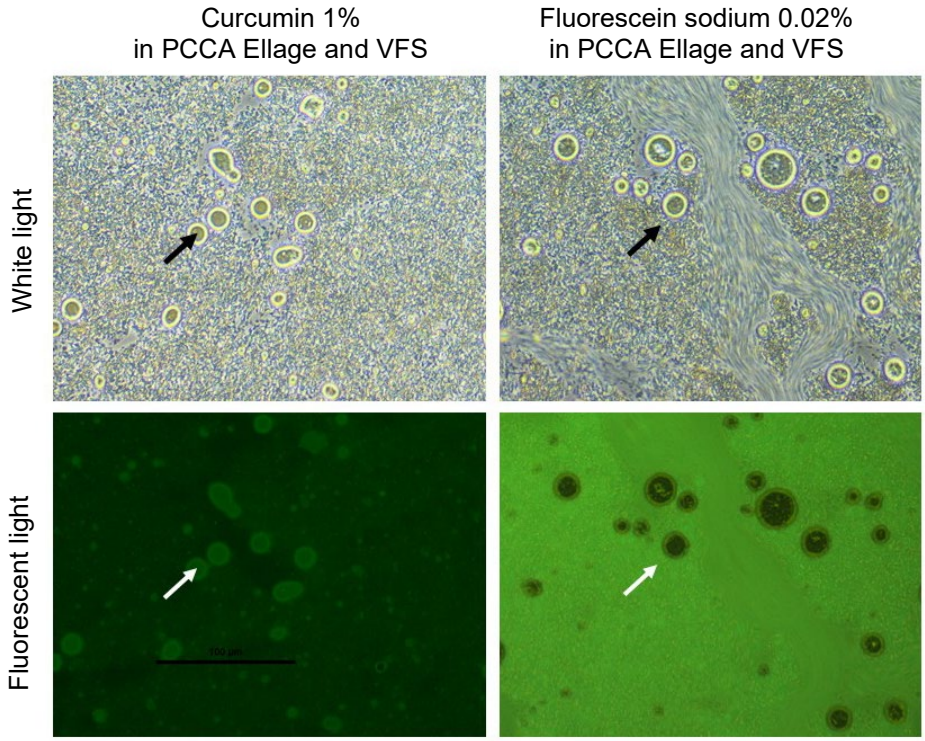

Figure 3. *Fluorescence microscopy (white and green fluorescent lights) for curcumin 1% and fluorescein sodium 0.02% in PCCA Ellage with VFS. Arrows highlight the interior of selected droplets for curcumin and the exterior of selected droplets for the fluorescein sodium, where the lipophilic and hydrophilic substances are respectively located.*

[1] Vasconcelos, T., Marques, S. and Sarmento, B. (2018) 'Measuring the emulsification dynamics and stability of self-emulsifying drug delivery systems'. *European Journal of Pharmaceutics and Biopharmaceutics*, 123 (1-8). doi:10.1016/j.ejpb.2017.11.003.

[2] Köllner, S., Nardin, I., Markt, R., Griesser, J., Prüfert, F. and Bernkop-Schnürch, A. (2017) 'Self-emulsifying drug delivery systems: Design of a novel vaginal delivery system for curcumin'. *European Journal of Pharmaceutics and Biopharmaceutics*, 115, p.268-75. doi:10.1016/j.ejpb.2017.03.012.