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Evaluation of In Vitro Performance Attributes of Imvexxy® (Estradiol) Vaginal Insert

Ghaled Hamad[1,2*], Megan Kelchen[2], Priyanka Ghosh[2], Tannaz Ramezanli[2], Sam G. Raney[2], Muhammad Ashraf[1], Ahmed S Zidan[1]

[1] Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality and [2] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

***CONTACT INFORMATION:** Ghaled.Hamad@fda.hhs.gov

PURPOSE

Imvexxy® (estradiol) vaginal inserts are small, light pink, tear-shaped inserts for manual placement into the vagina. The insert contains two components: a "shell" that encapsulate a "fill" formulation. In order to understand the effect of formulation and manufacturing process parameters on the quality and performance of such vaginal inserts, it is necessary to develop appropriate in vitro performance test methods that are sensitive and discriminating.

OBJECTIVES

This study aimed to develop appropriate in vitro performance test methods that are sensitive and discriminating and evaluate the critical performance attributes of vaginal inserts using Imvexxy® (estradiol) vaginal insert as a model drug product.

METHODS

The disintegration time of the shell of the insert was assessed at several agitation rates and using different volumes of simulated vaginal fluid (SVF). The disintegration time was recorded as the first appearance of the fill formulation in the SVF.

The distribution of estradiol between an oil phase and an external aqueous media (SVF) over 4 hours was studied at "high" and "low" concentrations. The diffusion rate of estradiol across the oil-aqueous interface between the two phases was determined from the slope of the concentration in receiver phase (oil phase or SVF) vs. time profile.

The release of estradiol from the insert emulsified in SVF and the extracted fill formulation emulsified in SVF at various stirring rates was evaluated using Franz diffusion cells. Additionally, in order to evaluate the impact of the emulsification on drug release, estradiol release from emulsified and non-emulsified fill formulation and inserts in presence and absence of disintegrated gelatin "shells" was also evaluated by the reverse dialysis method using Float-A-Lyzer cells.

The sensitivity of the reverse dialysis method to globule size of the emulsified fill formulation was evaluated after emulsifying the fill formulation using the M110P microfluidizer at various homogenization pressures to produce nanoemulsions of small, medium, and large globules.

RESULTS

❑ Disintegration time

- Disintegration of the "shell" occurred at the seam line.
- The disintegration time ranged from 2-60 minutes depending on the study conditions (agitation rates and media volume).
- The disintegration time was found to be inversely proportional to the agitation rate.

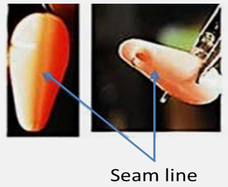

Fig 1. Disintegration of the "shell" in the SVF.

❑ Diffusion rate across oil-aqueous interface

- At both the high and low loading concentrations of estradiol, the diffusion rate of estradiol from aqueous SVF to the oil phase was greater than the diffusion rate of estradiol from the oil phase to the aqueous SVF. Therefore, it is hypothesized that estradiol will be spatially located within the emulsified oil droplets as the fill formulation is released and mixed with the vaginal secretions.
- A greater diffusion rate of estradiol from SVF to the oil phase was observed at the high loading concentration compared to the low loading concentration.

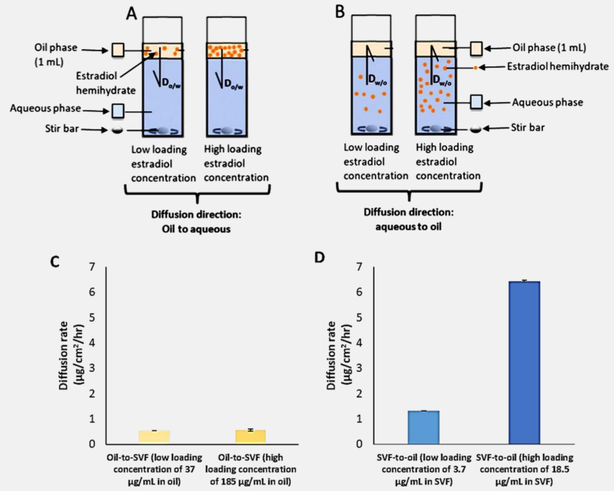

Fig 2. (A,B) Study design to evaluate the diffusion rate of estradiol over 4 hours. (C) Diffusion of estradiol from the oil phase to the aqueous phase ($D_{o/w}$) at low loading concentration (37 µg estradiol/1 mL of oil) and high loading concentration (185 µg estradiol/1 mL of oil). (D) Diffusion of estradiol from the aqueous phase to the oil phase ($D_{w/o}$) at low loading concentration (3.7 µg estradiol/1 mL of SVF) and high loading concentration (18.5 µg estradiol/1 mL of SVF) (n=3 replicates; mean ± SD).

❑ Release of estradiol at various stirring rates using Franz diffusion cells

- An increase in the release of estradiol from the emulsified fill formulation and emulsified insert was observed as the stirring rate increased.

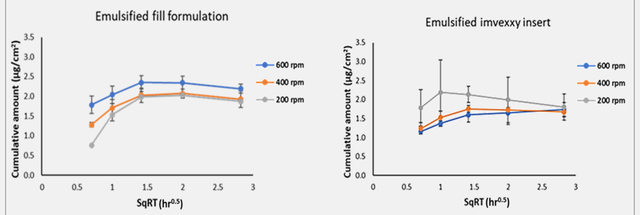

Fig 3. Cumulative amount of estradiol released versus square root of time at various stirring rates from either emulsified fill formulation (left) or emulsified insert (right) using Franz diffusion cells (n=3 replicates; mean ± SD).

❑ Effect of disintegrated gelatin shell on estradiol release using a reverse dialysis method

- The release of estradiol from the non-emulsified and emulsified fill formulation decreased in the presence of the disintegrated gelatin shell from the Imvexxy® product in the external media.

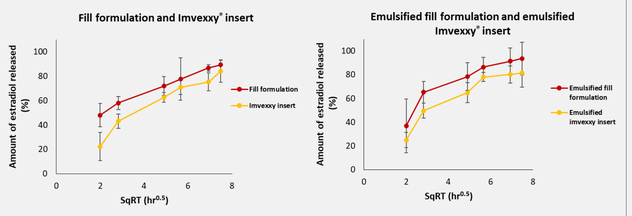

Fig 4. Percentage of estradiol released versus square root of time from either fill formulation and Imvexxy® insert (left) or emulsified fill formulation and emulsified Imvexxy® insert (right) using the reverse dialysis method (n=3 replicates; mean ± SD).

❑ Effect of globule size on estradiol release using the reverse dialysis method

- The release rates of estradiol from the fill formulation emulsified to small, medium, and large globule sizes were similar using the reverse dialysis method.

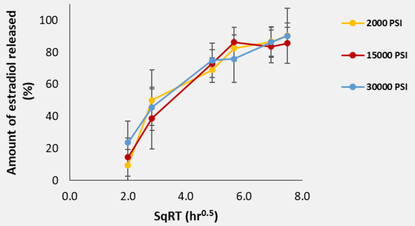

Fig 5. Percentage of estradiol released versus time from the emulsified fill formulation homogenized using the M110P microfluidizer at various homogenization pressures (2000, 15000, and 30000 PSI) to produce different globule sizes (Z-average (nm): 349.8, 228.3, 187,6 respectively) using the reverse dialysis method (n=3 replicates; mean ± SD).

CONCLUSIONS

This study revealed that the disintegration properties of the gelatin "shell" and the distribution and equilibration of drug among the two phases of the emulsified fill formulation may be critical performance characteristics of these vaginal inserts. Further studies are underway to investigate the effects of the critical material attributes and the microstructural properties of the emulsified formulations on the performance characteristics.

ACKNOWLEDGEMENT & DISCLAIMER

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