Development of an In Vitro Release Test Method for Miconazole Nitrate (MN) Vaginal Suppositories

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Introduction

To increase access to high quality vaginal drug products, the development of characterization-based bioequivalence (BE) approaches as an alternative to comparative clinical endpoint BE studies has become increasingly important. As part of a characterization-based BE approach for vaginal drug products, including vaginal suppositories, a validated in vitro release test (IVRT) can facilitate a comparison of release rates between a reference listed drug (RLD) product and a prospective generic drug product. The main objective of the present research was to develop and validate an IVRT method for vaginal suppositories.

Learning Objectives

1. Gain an understanding of key quality attributes of miconazole nitrate suppositories.
2. Develop an IVRT method for vaginal suppositories.

Methods

Monistat 3® (miconazole nitrate, MN) vaginal suppository, 200 mg was chosen as the RLD. Following gas chromatograph-mass spectrometry (GC-MS) analysis, Suppocire® AM, which has a similar hydrocarbon composition to the RLD, was used to prepare laboratory-made suppositories (LMS). Comprehensive physicochemical characterization (i.e., drug content, rheology, melting range, particle size distribution, and disintegration) of the LMS and RLD was conducted. An IVRT method using a vertical diffusion cell (VDC) apparatus at 37°C was developed. The receptor solution and membrane were evaluated. Following the method development, sodium acetate buffer (pH 4.2) with 0.45% sodium lauryl sulfate, 5% glucose and 0.018% bovine serum albumin and a polyethersulfone membrane (0.8 µm) were selected as the receptor solution and membrane, respectively. The reproducibility and the sensitivity of the IVRT method were assessed (n=3-6 cells/run).

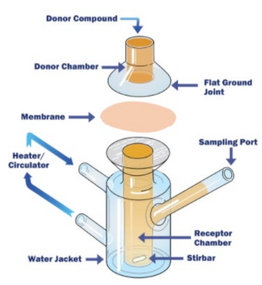


Image from PermeGear website (https://permegear.com/v-series/v6-vs/ and permegear.com/franz-cells/)

Results

- Rheology of MN suppositories

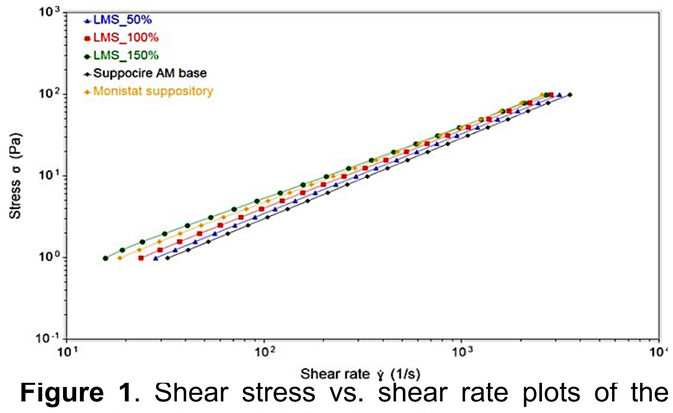


Figure 1. Shear stress vs. shear rate plots of the blank suppository base, LMS with different strengths, and the RLD product (n=3), depicting Newtonian behavior.

Table 1. Viscosities of the blank suppository base and MN suppository formulations at 37°C (TA HR-2 rheometer, 40.0 mm cone and plate,1.98°) (Mean±SD, n=3).

Sample	Percent of label claim	Viscosity (Pa.s)
LM suppository (4%, w/w)	50%	0.0336 ± 0.0006
LM suppository (8%, w/w)	100%	0.0378 ± 0.0018
LM suppository (12%, w/w)	150%	0.0557 ± 0.0051
Suppocire® AM Base	-	0.0292 ± 0.0004
Monistat® suppository (8%, w/w)	-	0.0391 ± 0.0022

- IVRT method reproducibility

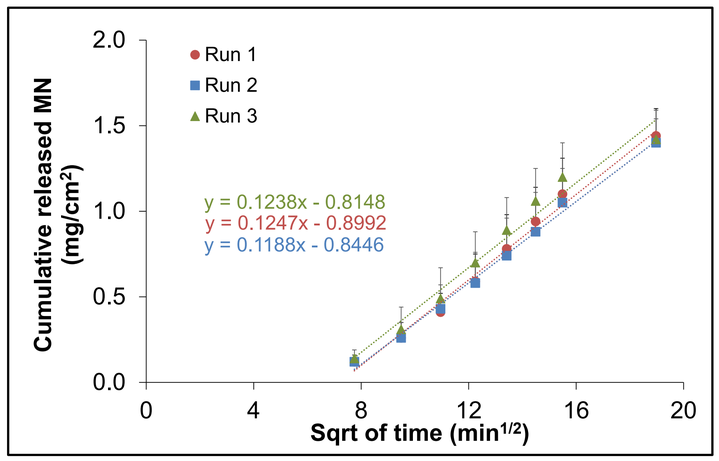
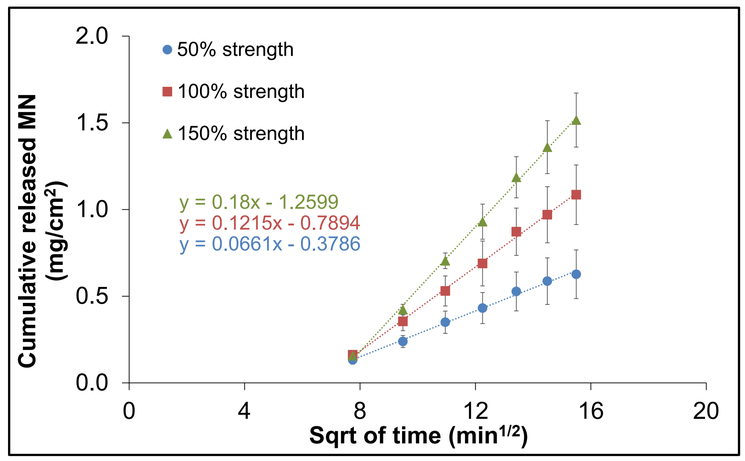


Figure 2. Linear regression (the Higuchi model) of the IVRT profiles of Monistat® 3 suppository obtained using a VDC apparatus at 37°C with a sodium acetate buffer (50 mM, pH 4.2) with 0.45% sodium lauryl sulphate, 5% glucose and 0.018% bovine serum albumin receptor solution (n=6 cells/run, 3 runs; mean±SD).

Table 2. In vitro release rate (6-hr) of RLD suppository calculated using the Higuchi model (mean ± SD, n=6 per run). Good reproducibility was observed with inter- and intra-day CV%<15%.

	Run 1	Run 2	Run 3	Mean
Release rate (6-hr) (mg/cm²/min^1/2)	0.1247 ± 0.0153	0.1185 ± 0.0124	0.1241 ± 0.0130	0.1224 ± 0.0131

- IVRT method discriminatory ability



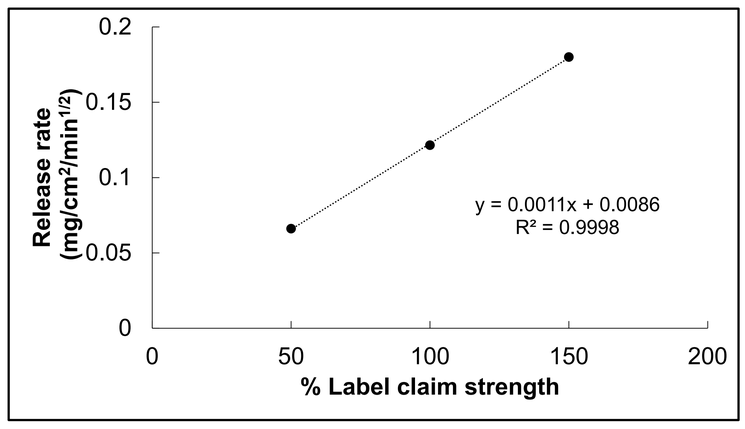


Figure 3. In vitro MN release rates of laboratory-made MN suppositories with 50%, 100% and 150% of the label claim strength analyzed using the Higuchi model (sensitivity (top), 1-4 hr duration) (mean±SD, n=6). Correlation between the drug concentration and average in vitro drug release rate (1-4 hr) analyzed using the Higuchi model shows good linearity with R^2 > 0.97 (specificity (bottom)).

Conclusions

To facilitate the development of a characterization-based BE approach for vaginal suppositories, a reproducible and sensitive IVRT method was developed. Additional research is planned to identify critical material attributes of MN vaginal suppositories with/without gelatin coating.

Acknowledgement

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