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Understanding Critical Quality Attributes of Gelatin Coated Miconazole Nitrate Vaginal Inserts and Suppositories

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PURPOSE

The bioequivalence (BE) of a locally-acting generic vaginal insert or suppository product to its brand name drug is typically established using a comparative clinical endpoint BE study. The development of in vitro characterization-based BE approaches for vaginal inserts and suppositories may enhance patient access to generics for these vaginal dosage forms. Two common types of locally-acting inserts/suppositories are those composed of a drug-containing hard fat base and those wherein a gelatin coating encapsulates the drug and inactive ingredients. To support the development of characterization-based BE approaches for such products, an understanding of the microstructure of the different insert and suppository types and the impact of the microstructure on drug release is necessary. The present work aims to investigate the critical quality attributes (CQA) of uncoated and gelatin-coated vaginal inserts and suppositories to facilitate the development of a characterization-based BE approach for such drug products.

METHODS

Monistat 3 miconazole nitrate (MN) vaginal suppository, 200 mg, which includes a “core” encapsulated by a gelatin shell, was chosen as the gelatin-coated formulation (referred to as “MN insert”). Monistat 3® MN vaginal suppository, 200 mg, which is an uncoated suppository, was chosen as the uncoated control (“MN suppository”). Comparative characterization of the MN insert and MN suppository was carried out to delineate the quality attributes of the gelatin coated formulation, including gas chromatograph-mass spectrometry (GC-MS) to analyze the hydrocarbon composition of the MN insert core and MN suppository; differential scanning calorimetry (DSC) to understand the thermal behavior of the MN insert core and MN suppository; a rheometer to determine viscosity profiles and melting range; and 3-D X-ray microscopy (XRM) to characterize the inner structure of MN insert core and MN suppository and the gelatin coat thickness of the MN insert. Moreover, MN particles were imaged using polarized light microscopy (PLM) and particle size distribution (PSD) was analyzed using ImageJ. Surface dissolution imaging (SDi2) was utilized to understand the impact of the gelatin coating on drug dissolution from the MN insert and MN suppository. Disintegration time (DT) of the MN insert and MN suppository was determined using an automatic disintegration tester at 37°C. The in vitro release of MN from the insert core and suppository were evaluated using a vertical diffusion cell (contact area: 1.77 cm^2) at 37°C with a receptor solution of simulated vaginal fluid (SVF) containing 0.45% (w/v) sodium laureth sulfate.

RESULTS

➢ Drug Content & Uniformity

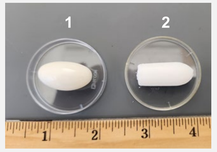

Figure 1. MN content in three sections from the (1) MN suppository and (2) MN insert products (n=3 replicates from 3 independent units; mean±SD).

➢ Hydrocarbon Analysis

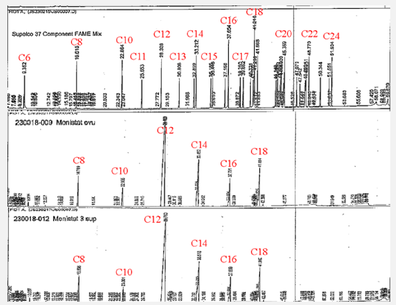

Figure 2. GC/MS chromatograms of FAME 37 mix (standard, top), MN insert (middle), and MN suppository (bottom).

Table 1. Hydrocarbon compositions of the marketed MN products.

	Fatty Acid Composition (mg/g)	
	MN insert	MN suppository
C8	12.6	13.4
C10	10.4	11.6
C12	110.4	124.7
C14	20.7	23.3
C16	6.62	7.14
C18	20.7	25.2
C20	ND	ND

ND: Not detected

➢ 3D X Ray Microscopy

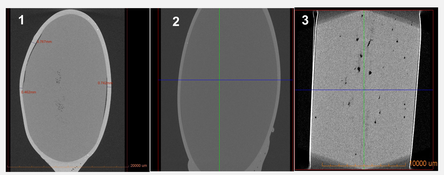

Figure 3. Representative 3D X-ray microscopic images of the (1) MN insert showing the gelatin coat thickness; and transverse section from the mid part of (2) MN insert and (3) MN suppository.

➢ Particle Size Distribution of MN

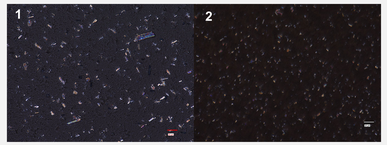

Figure 4. PLM images of MN crystals in the (1) MN insert and (2) MN suppository product Scale bar=20 µm.

Table 2. Particle size analysis results.

	Count	Length (µm)	Width (µm)	D10	D50 (Length, µm)	D90 (Length, µm)	Span
MN Insert	1871	6.32 ± 4.57	3.45 ± 2.08	2.00	5.20	12.48	2.01
MN suppository	6240	3.46 ± 2.09	2.04 ± 1.16	1.50	2.90	6.10	1.58

➢ Rheological Properties

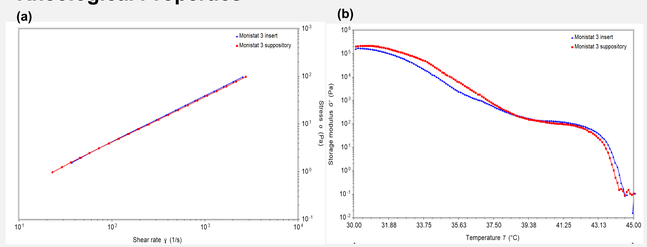

Table 3. Viscosities and melting range of the MN insert and suppository products at 37°C with a core and plate geometry (40 mm, 1.99˚) at a gap of 120 µm (n=3, mean±SD).

Sample	Viscosity (Pa s)	Melting Range (°C)
MN suppository	0.03631 ± 0.0351	32.89. ± 0.22 - 44.83 ± 0.14
MN insert core	0.04216 ± 0.0031	31.11 ± 0.10 - 44.87 ± 0.27

➢ Surface Dissolution Imaging

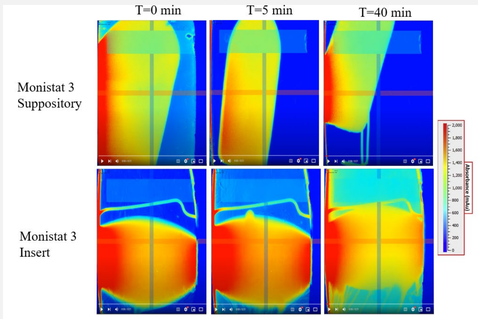

Figure 6. Representative SDi2 images of the MN insert and MN suppository during a 24-hour dissolution study in the SVF at 37˚C (open-loop, 20 mL/ min for 1 hour followed by closed-loop, 5 mL/min for 23 hours).

➢ Disintegration Time

Table 4. Disintegration time of the MN insert and MN suppository products in SVF at 37˚C (n=6, mean±SD).

Disintegration Time (min)	
MN insert	**MN suppository**
7.25 ± 0.36	3.45 ± 0.33

➢ In Vitro Release Study

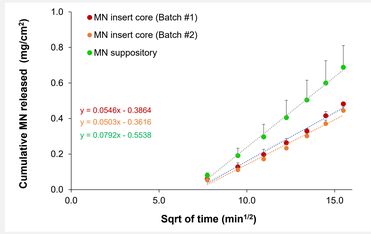

Figure 8. Cumulative release of MN per area versus square root of time (1-4 hours) from two batches of the MN insert core and one batch of the MN suppository obtained using a vertical diffusion method (contact area: 1.77 cm^2) at 37°C in SVF containing 0.45% (w/v) sodium laureth sulfate (n=3 or 5, mean±SD).

CONCLUSION

The present study delineated the key quality attributes of the gelatin coated MN insert. The MN insert core showed similar physicochemical and rheological properties to the MN suppository. The gelatin coating of the MN insert does not appear to impede MN release significantly when visualized using a flow through method via SDi2. Further studies are being conducted to evaluate the in vitro drug release from the MN insert and MN suppositories using an in vitro release test study. Additionally, studies to prepare and characterize laboratory-made MN inserts with a comparable hydrocarbon composition to the MN insert core are ongoing. Finally, future studies will evaluate the impact of material attribute differences (e.g., gelatin grade) on in vitro MN release from insert formulations.

ACKNOWLEDGEMENT

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