Impact of Material Attributes on In Vitro Release Characteristics of Rectal Suppositories

Lingxiao Xie[1], Weizhou Yue[1], Megan Kelchen[2], Priyanka Ghosh[2], Mengmeng Niu[2], Sam G. Raney[2], Jie Shen[1,3]
[1] University of Rhode Island, College of Pharmacy, Kingston, Rhode Island, 02881
[2] Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993
[3] University of Rhode Island, College of Engineering, Kingston, Rhode Island, 02881

➢ *Introduction:*

Unlike topical dermatological semisolid drug products, characterization-based bioequivalence (BE) approaches for locally-acting rectal suppositories that can mitigate the risks associated with potential failure modes for BE have yet to be established. The selection of the suppository base, in addition to the manufacturing process, may impact physicochemical and structural characteristics of suppositories, resulting in different in vitro drug release rates between a test and reference product. Therefore, it is essential to understand the influence of critical material attributes (CMA) on critical quality attributes (CQA) and in vitro release characteristics of rectal suppositories to support the development of characterization-based BE approaches for such products.

➢ *Methods:*

Mesalamine rectal suppositories were selected as the model drug for the project. Two commercial products, CANASA® (mesalamine) rectal suppository, 1 gram (reference product) and an approved generic product, were evaluated. Laboratory-prepared mesalamine rectal suppositories composed of various bases, including Witepsol® H15 (from two sources) and Witepsol® H35, were prepared using a hot-melt-mixing method. The physicochemical and structural properties (e.g., drug content, viscosity, melting temperature range, and particle size of mesalamine in suppository bases) of the commercial and laboratory-prepared (LP) suppositories were characterized. Fatty acid composition of the suppositories was determined via gas chromatography-mass spectrometry (GC-MS). An in vitro release test (IVRT) was conducted using a vertical diffusion cell (VDC) system at 37ºC.

➢ *Results:*

- Commercial and LP suppositories composed of different bases (Witepsol® H15 vs. H35) had a similar drug loading (~33% w/w) (**Figure 1**), viscosity (~0.1 Pa·s at 37ºC) and melting range (33-39ºC) (**Table 1,** next slide).

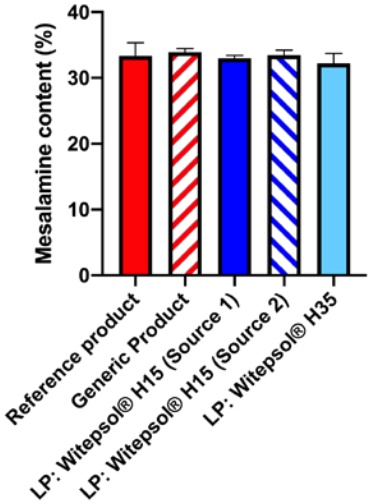


Figure 1. Mesalamine content of melamine suppositories (*n*=3, mean±SD).

THINK BIG WE DO℠

THE UNIVERSITY OF RHODE ISLAND

CONTROLLED RELEASE SOCIETY CRS 2021 VIRTUAL ANNUAL MEETING

Impact of Material Attributes on In Vitro Release Characteristics of Rectal Suppositories

Lingxiao Xie[1], Weizhou Yue[1], Megan Kelchen[2], Priyanka Ghosh[2], Mengmeng Niu[2], Sam G. Raney[2], Jie Shen[1,3]
[1] University of Rhode Island, College of Pharmacy, Kingston, Rhode Island, 02881
[2] Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993
[3] University of Rhode Island, College of Engineering, Kingston, Rhode Island, 02881

➢ *Results:*

Table 1. Viscosity and melting range of mesalamine suppositories (*n*=3, mean±SD).

Mesalamine suppository	Viscosity (37ºC, Pa.s)	Melting Range (ºC)
Reference product	0.097±0.0012	32.9±0.41 ~ 37.3±1.38
Generic product	0.114±0.0006	33.2±0.10 ~ 38.8±0.22
LP: Witepsol® H15 (Source 1)	0.120±0.0067	33.7±0.01 ~ 36.6±0.72
LP: Witepsol® H15 (Source 2)	0.138±0.0024	33.8±0.42 ~ 37.4±0.78
LP: Witepsol® H35	0.116±0.0144	32.3±0.41 ~ 36.7±1.89

- The mesalamine particle size of the commercial and LP suppositories was generally larger (d_{50}: ~30 µm) than that of the generic product (d_{50}: ~27.1 µm) (**Table 2** and **Figure 2**).

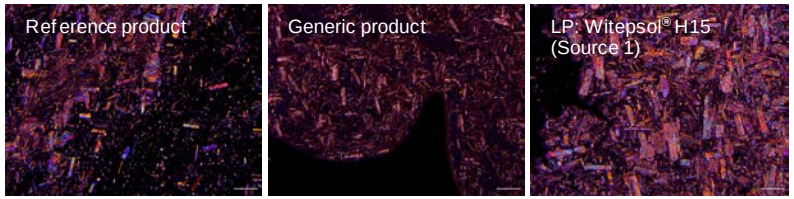


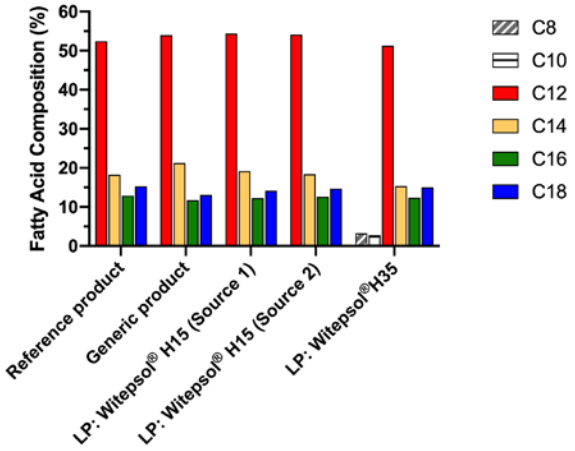
Figure 2. Polarized light microscopy images of commercial mesalamine suppositories and mesalamine in a suppository base (Witepsol® H15 (Source 1). Scale bar=100 µm.

Table 2. Particle size analysis results

Mesalamine suppository	Particle diameter (length, µm)			
	D10	D50	D90	Span
Reference product	19.6	30.2	72.6	1.75
Generic product	28.1	27.1	61.3	1.23
LP: Witepsol® H15 (Source 1)	19.2	30.6	76.2	1.86

- The commercial products and Witepsol® H15 suppositories were primarily composed of C12, C14, C16 and C18 fatty acids, whereas Witepsol® H35 suppositories also contained C8 and C10 fatty acids (**Figure 3**).

Figure 3. Fatty acid compositions of mesalamine suppositories analyzed using GC-MS.



THE UNIVERSITY OF RHODE ISLAND

CONTROLLED RELEASE SOCIETY CRS 2021 VIRTUAL ANNUAL MEETING

Impact of Material Attributes on In Vitro Release Characteristics of Rectal Suppositories

Lingxiao Xie[1], Weizhou Yue[1], Megan Kelchen[2], Priyanka Ghosh[2], Mengmeng Niu[2], Sam G. Raney[2], Jie Shen[1,3]
[1] University of Rhode Island, College of Pharmacy, Kingston, Rhode Island, 02881
[2] Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993
[3] University of Rhode Island, College of Engineering, Kingston, Rhode Island, 02881

➢ *Results:*

- Differences in the in vitro drug release rates were observed among the reference product, generic product, and various LP suppositories (**Figure 4** and **Table 4**).

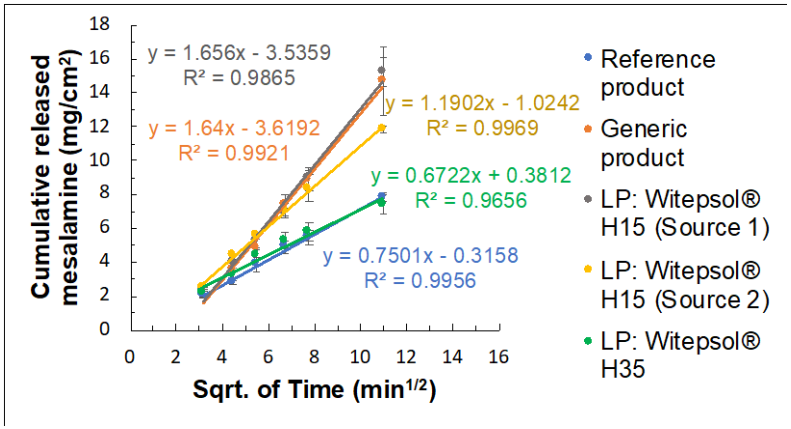


Figure 4. In vitro release profiles of mesalamine suppositories obtained using a VDC apparatus at 37ºC in 0.2 M phosphate buffer (pH 7.4) (*n*=3).

Table 4. In vitro release rates of mesalamine suppositories analyzed using the Higuchi model (*n*=3, mean±SD).

Mesalamine suppository	Release rate (mg/cm²/min^1/2)
Reference product	0.75±0.029
Generic product	1.64±0.215
LP: Witepsol® H15 (Source 1)	1.66±0.102
LP: Witepsol® H15 (Source 2)	1.19±0.014
LP: Witepsol® H35	0.67±0.038

➢ *Conclusions:*

An understanding of the impact of CMAs on the CQAs and the drug release characteristics of rectal suppositories can facilitate the development of characterization-based BE approaches for rectal suppository products. This research demonstrated that the CMAs (i.e., suppository base composition) may influence the drug release from mesalamine suppositories when assessed by an IVRT. Additional research is planned to further develop the IVRT study design and evaluate the impact of CQAs on the drug release rate from suppositories.

➢ *Acknowledgement:*

This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a grant (U01FD006721) totaling $500,000 with 100 percent funded by FDA/HHS. The views are those of the author(s) and do not necessarily represent the official views of , nor an endorsement, by FDA/HHS, or the U.S. Government.

CONTACT INFORMATION: Dr. Jie Shen (jie_shen@uri.edu) University of Rhode Island

THE UNIVERSITY OF RHODE ISLAND

FDA U.S. FOOD & DRUG ADMINISTRATION

THINK BIG WE DO℠

THE UNIVERSITY OF RHODE ISLAND

CONTROLLED RELEASE SOCIETY CRS 2021 VIRTUAL ANNUAL MEETING