Development of an In Vitro Release Testing Method for Rectal Suppositories

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PURPOSE

Rectal suppositories account for more than 40% of the FDA-approved dosage forms that are administered using the rectal route. Currently, the bioequivalence (BE) of rectal suppositories is often established through BE studies with pharmacokinetic endpoints. The development of characterization-based BE approaches for rectal suppositories would systematically mitigate the risks of potential failure modes for BE by ensuring that there is no difference (relative to the reference product) in the components, composition or other aspects of the formulation, and by verifying the equivalent performance of the test and reference products in vitro and/or in vivo. As part of a characterization-based BE approach, a reproducible, validated and discriminatory in vitro release test (IVRT) for rectal suppositories would facilitate a comparison of release rates between a reference drug product and a prospective generic drug product. The main objective of the present study was to develop a reproducible and discriminatory IVRT method for rectal suppositories.

METHODS

Mesalamine rectal suppositories were chosen as model drug products in the present research. CANASA® (mesalamine) rectal suppository, one gram was selected as the reference product. Laboratory-prepared mesalamine rectal suppositories composed of Witepsol® H15 were prepared using a hot melt mixing method. The molten mixture was transferred to disposable suppository molds and sealed after a cooling process. The physicochemical properties (e.g., drug content, rheological properties, melting temperature, polymorphic transitions, and particle size of mesalamine) of the laboratory-prepared suppositories and the reference product were characterized. IVRT studies of mesalamine suppositories were conducted using a vertical diffusion cell (VDC). The temperature at the surface of the membrane was maintained at 37°C. The selection of IVRT study parameters such as the receptor solution and membrane were investigated. Following the initial method development studies, phosphate buffer (0.2 M, pH 7.5) was selected as the receptor solution and a polyethersulfone (PES) membrane (0.45 µm) was used as the membrane. Two sample loading methods (either loading pieces of a suppository or an intact suppository with customized dimensions) were evaluated. Following method development, the reproducibility of the IVRT method was evaluated using the reference product (n=6 cells/run, 3 independent runs). The discriminatory ability of the method was evaluated using laboratory-prepared mesalamine suppositories manufactured with different strengths (n=6 cells/strength).

RESULTS

➢ *Physicochemical properties of mesalamine rectal suppositories*

- *Drug content and uniformity*

RLD product: CANASA®

Laboratory-prepared formulation

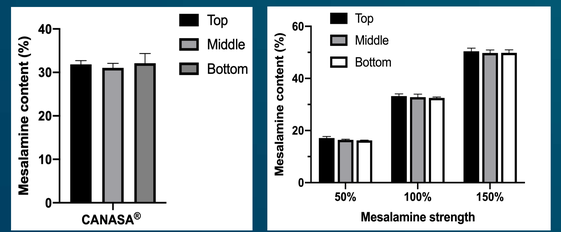

Figure 1. Average mesalamine content in three sections of three suppositories from the marketed product (left) and laboratory-prepared suppositories (right) (mean ± standard deviation (SD), *n*=3).

- *Morphology and particle size*

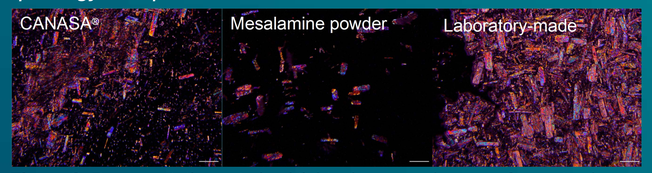

Figure 2. Representative polarized light microscopy images of mesalamine powder and mesalamine suppositories. Scale bar=100 µm.

Table 1. Particle size analysis results (mean ±SD, *n*=3).

	Count	Length (µm)	Width (µm)	D10 (Length, µm)	D50 (Length, µm)	D90 (Length, µm)	Span
Mesalamine Powder	542	37.1±21.68	24.5±14.90	19.2	30.4	63.3	1.45
CANASA® (RLD)	1998	39.6±26.31	27.2±18.47	19.6	30.2	72.6	1.75
Laboratory-prepared	1570	40.2±26.52	26.5±16.67	19.2	30.6	76.2	1.86

- *Melting behavior*

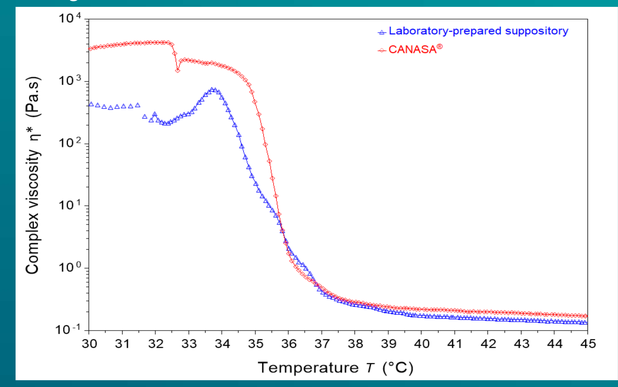

Figure 3. The melting range of the marketed suppository product and laboratory-prepared suppositories characterized by rheometer.

Table 2. Average melting ranges of mesalamine suppositories (mean ± SD, *n*=3).

Mesalamine suppositories	Melting range (°C)
CANASA® (RLD)	32.9±0.41-37.3±1.38
Laboratory-prepared	33.7±0.17-37.1±0.16

➢ *In vitro release test (IVRT) method development*

- *Study conditions*

Apparatus: Vertical Franz diffusion cell (VDC)
- Contact area: 1.77cm²
- PES membrane (0.45 µm)
- Membrane temperature: 37ºC
- Release medium: phosphate buffer (0.2 M, pH 7.5)
- Sample loading method: Suppository pieces

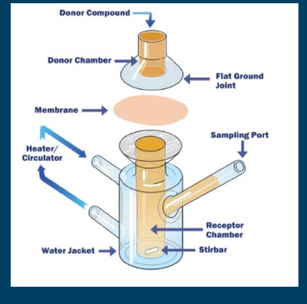

Image from PermeGear website (permegear.com/franz-cells/)

- *Reproducibility study of VDC method*

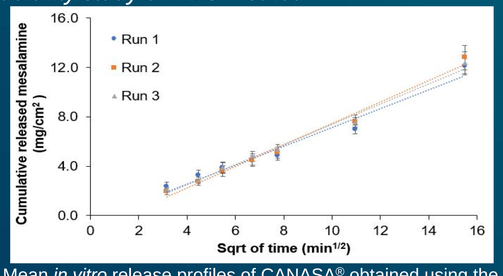

Figure 4. Mean *in vitro* release profiles of CANASA® obtained using the developed VDC method at 37°C (three runs, *n*=6 per run).

Table 3. *In vitro* release rate (4-hr) of CANASA® calculated using the Higuchi model (mean ± SD, *n*=6 per run). Good reproducibility with inter- and intra-day CV%<15%.

	Run 1	Run 2	Run 3	Mean
Release rate (4-hr) (mg/cm²/min^1/2)	0.761±0.047	0.867±0.087	0.815±0.092	0.814±0.053
CV (%)	6.22	10.03	12.22	6.47
Drug depletion (%)	43.6±2.18	44.0±3.49	43.4±3.89	43.3±0.70
CV (%)	5.12	7.92	8.98	1.61

- *Discriminatory ability study of VDC method*

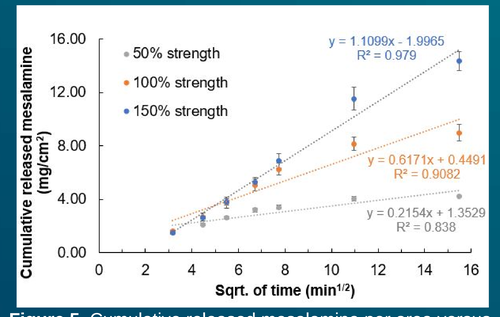

Figure 5. Cumulative released mesalamine per area versus square root of time (4-hr) of laboratory-made suppositories (mean ± SD, *n*=6 per strength).

CONCLUSIONS

Consideration may be given for a characterization-based BE approach for rectal suppositories to include IVRT studies to demonstrate equivalent drug release rates of a prospective generic drug product compared to a reference product. The IVRT method using the VDC apparatus demonstrated good reproducibility and discrimination in an IVRT evaluating suppositories containing mesalamine, illustrating the feasibility of such an IVRT for suppositories.

ACKNOWLEDGEMENT

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