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In Vitro Release Test (IVRT) Comparisons of Six Acyclovir Cream, 5% Products to Evaluate the Impact of Compositional Differences on Product Performance

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PURPOSE

Sensitive and discriminating product characterization tests help to evaluate whether a prospective generic topical product would have the same performance as a Reference Listed Drug (RLD) product. Among these characterization tests, the **in vitro release test (IVRT) is a compendial performance test method** for topical semisolid drug products that could collectively be used for this purpose.
The research reported here was part of a larger research project that characterized the quality and performance of multiple acyclovir cream, 5% products to identify sensitive in-vitro tests to discriminate differences between a prospective generic product compared to its RLD product that may have the potential to impact in vivo product performance.

OBJECTIVE

The objective of the work presented here was to use a validated IVRT method to screen multiple, compositionally different acyclovir cream, 5% products (marketed in different countries) in order **to identify the product(s) that could serve as the negative control(s) for bioequivalence (BE)** in other research studies that were part of a larger research project.

METHODS

- Validated IVRT method (Tiffner et. al, 2018)
  - Hanson Microette™ vertical diffusion cell (VDC) system
    -> 6 x 12 mL VDCs (Orifice Ø 15 mm)
    -> Receptor medium: 0.9% sodium chloride solution (at 32°C and stirred 600 rpm)
    -> Tuffryn® membrane (pore size: 0.45 µm)
    -> Sampling times: 0.5, 1, 2, 3, 4, 5 and 6 hours
  - Analytical method: HPLC-UV
- Reference product
  - R1/R2: ZOVIRAX® cream 5% (GSK, distributed by Valeant Pharmaceuticals, USA)
- Test products
  - T1 ZOVIRAX cream 5% (GSK, Austria)
  - T2 ZOVIRAX cream 5% (GSK, UK)
  - T3 ACICLOSTAD cream 5% (STADA, Austria)
  - T4 Aciclovir 1A Pharma® cream 5% (1A Pharma, Austria)
  - T5 Antiviral Cold Sore cream 5% (Boots, UK)
- Pairwise comparison each using 6 VDCs each:
  - Positive control: R1 versus R2
  - R1 versus T1/T2/T3/T4/T5
- Statistical analysis
  - Pairwise comparisons of the release rates according to USP general chapter<1724>: Calculated confidence interval (CI) must lie within the equivalence limits of 75 and 133.33% to confirm equivalence.

RESULTS

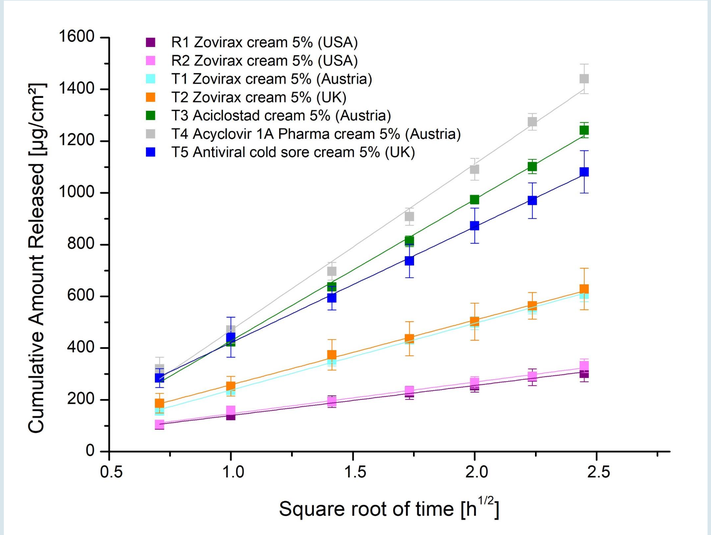

Figure 1: *Release rate profiles for the reference product (R1, R2) and the 5 test products (T1-T5).*

Release rate profiles showed that the test products (T1-T5) were distinctly different from the reference product (R1, R2). Based on the pre-specified equivalence limits of 75 – 133.33% using IVRT, all the Test acyclovir cream, 5% products evaluated in this study were found to have a drug release rate that was "inequivalent" to that of the Reference product. The release rate from the Reference product ZOVIRAX® (acyclovir) cream, 5% U.S. was found to be equivalent to itself when compared in two separate IVRT runs (85.73-103.02%).

Table 1 : *Equivalence comparisons*

Pairwise Comparisons	CI [%]		Equivalence
	Lower Limit	Upper Limit	
Positive Control: R1 versus R2	85.73	103.02	YES
R1 versus T1	40.10	48.45	NO
R1 versus T2	41.57	51.19	NO
R1 versus T3	18.78	23.43	NO
R1 versus T4	16.27	19.60	NO
R1 versus T5	23.33	28.55	NO

CONCLUSIONS

- The validated IVRT method utilized in this study successfully demonstrated that the release rates for the positive controls for BE (i.e., a comparison of the ~~RLD~~ Reference product to itself) were equivalent, demonstrating the accuracy and reproducibility of the IVRT method.
- **All test products** (T1-T5) were found to have release rates that were inequivalent to that of the Reference product, **suggesting that any of them might serve as a negative control for BE.**
- Based on these IVRT results in this study and on corroborating results from an in vitro permeation test studies using excised human skin (data not shown), **Aciclovir 1A Pharma® cream, 5%** was the most different and was therefore **used as the designated negative control** in an in vivo BE study in human subjects. The differences in acyclovir release rate observed in this IVRT study corresponded with differences in bioavailability in vivo, and the results of that study in human subjects suggested that Austrian Aciclovir 1A Pharma® cream, 5% would not be BE to the U.S. RLD product (*Bodenlenz et al. (2017) Clin Pharmacokinet 56(1):91-98).*

FUNDING / REFERENCE

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