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Comparative In Vitro Release Tests (IVRT) Of Seven Topical Acyclovir Products Using A Validated IVRT Method With A Vertical Diffusion Cell (VDC) Apparatus

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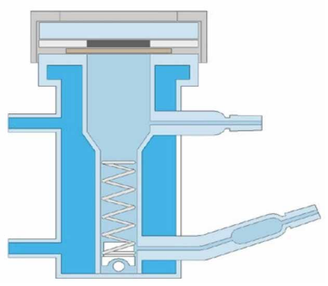
Purpose

Release of the active pharmaceutical ingredient (API) from its formulation is a key parameter for the API to become bioavailable. In vitro release testing (IVRT) using VDC apparatus is a useful method to assess this release.

The aims of this study were to perform a comprehensive qualification of the VDC apparatus, to validate the IVRT method, and to compare the in vitro release rate of acyclovir from seven different topical acyclovir 5% drug products.

Material & Methods

IVRT method and VDC apparatus (Hanson Research Corporation, USA):



- 6 VDCs in parallel (VDC Volume: 12 mL; Orifice: 15 mm)
- Stirring speed: 600 rpm
- Receptor medium temp.: 32°C
- Nominal amount applied: 300 mg
- Tuffryn® membrane
- Receptor medium: 0.9% sodium chloride solution
- Sampling times: 0.5, 1, 2, 3, 4, 5 and 6 hours
- Analytical method: HPLC-UV

Figure 1: *Hanson VDC (source: https://hansonresearch.com)*

Apparatus Qualification: Evaluation of the capacity and the diameter of the VDCs, the temperature of the receptor medium, the stirring speed, the dispensed sampling volume and the environmental conditions.

Method Validation: Evaluation of the membrane inertness (binding), acyclovir solubility in receptor medium and linearity, precision, reproducibility, recovery, and robustness of the IVRT method. Zovirax cream 5% (GSK, AT), a 2.5%, 5.0 and 10.0% acyclovir cream prepared in house were used for the study.

Comparative IVRT Study: Release rate comparisons between the reference product (R) and six test products (P1-P6) were performed using the Mann-Whitney U test described in USP general chapter <1724>.

Results

Apparatus Qualification

Table 1: *Apparatus qualification: 5 of 6 parameters were successfully validated Parameter 1 – the capacity of the VDC cell – was 9.77 ± 0.13 mL instead of the nominal 12 mL. The measured volume of 9.77 mL was used for further calculation.*

Parameter	Passed
P1: Capacity of the cells	✗
P2: Diameter of the orifice of the cell	✓
P3: Temperature of the receptor medium	✓
P4: Speed of the magnetic stirrer	✓
P5: Dispensed sampling volume	✓
P6: Environmental conditions	✓

Comparative IVRT Study

None of the six test products showed equivalent release rates compared to the reference product (Figure 3). Statistical evaluation showed that none of the computed confidence intervals for the five comparisons lies within the limits of 75.00% and 133.33% (Table 3).

Table 2: *Comparative IVRT study*

Pairwise comparison	Computed confidence interval	
	Lower Limit	Upper Limit
R versus P1	0.38159	0.47777
R versus P2	0.041619	0.053367
R versus P3	0.19362	0.25324
R versus P4	0.16410	0.21423
R versus P5	0.23334	0.28553
R versus P6	0.41574	0.51190

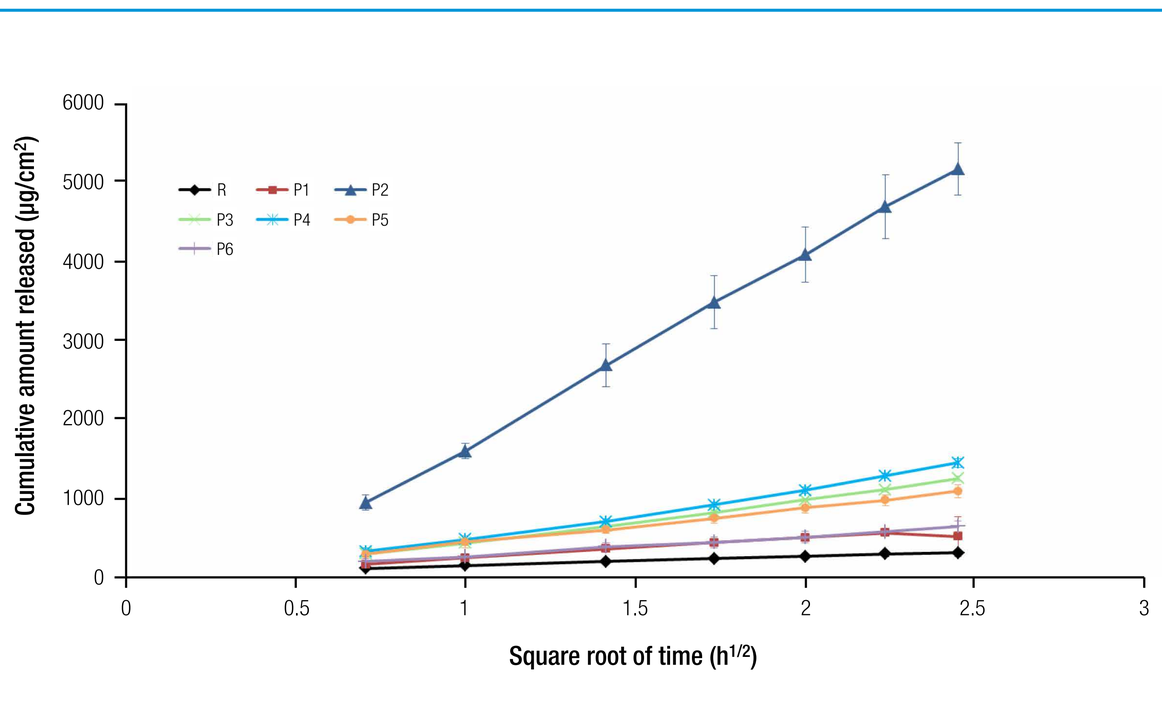


Figure 2: *Cumulative amount released versus square root of time for the reference product R and the 6 test products (each product dosed on 6 VDCs)*

IVRT Method Validation

Table 3: *IVRT method validation: all parameters were successfully validated*

Parameter	Acceptance Criteria	Passed
Membrane Inertness	No acyclovir binding on the membrane: Recovery of 105.5%	✓
Receptor medium solubility	Solubility > 10 times higher than the maximum acyclovir concentration in the receptor medium observed during the IVRT study	✓
Linearity	Lowest R^2 : 0.97, no outlier	✓
Precision and Reproducibility	Inter-run variability 5.8%; intra-run variability 4.4%	✓
Sensitivity	Mean release rate increased with increasing acyclovir concentration	✓
Specificity	Linear regression model (release rate versus product concentration) R^2 =0.943	✓
Selectivity	IVRT method accurately identify in-equivalent and equivalent acyclovir products	✓
Robustness	Release rate for temperature and stirring speed variation deviate < 15%	✓
Recovery	< 10%; no excessive acyclovir depletion	✓

Conclusion

The routine implementation of an apparatus qualification and a method validation supports the quality and reproducibility of IVRT studies. This IVRT study demonstrated that a validated IVRT method is an effective tool for detecting differences in release rates of the API and for evaluation of formulations.

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