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Comparative In Vitro Release of Six Different Topical Acyclovir Products Using a Vertical Diffusion Cell (VDC) Apparatus

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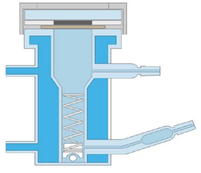
Purpose

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 determine 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 of acyclovir from six different topical acyclovir 5% drug products.

Material & Methods

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.The measured volume was used.



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 temperature: 32°C
- Nominal amount applied: 300 mg
- Tuffryn® membrane (pore size: 0.45 µm)
- Receptor medium: 0.9% sodium chloride solution
- Sampling times: 0.5, 1, 2, 3, 4, 5 and 6 hours
- Analytical method: HPLC-UV
- Receptor sample volume: 500 µL sample aliquots

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

Method validation: Evaluation of the membrane inertness (binding), acyclovir solubility in receptor medium and linearity, precision, reproducibility, recovery, and robustness of the IVRT method.

Comparative IVRT study was conducted according to the USP general chapter <1724>. The acyclovir release rate comparisons between the reference product and the test products were performed using the "Wilcoxon Rank Sum/Mann-Whitney statistical test" as described in USP <1724>.

Following products were compared:

Reference product:
- Acyclovir cream 5% (Reference Product)

Test products:
- Acyclovir cream 5% (Test Product 1)
- Acyclovir ointment 5% (Test Product 2)
- Acyclovir cream 5% (Test Product 3)
- Acyclovir cream 5% (Test Product 4)
- Acyclovir cream 5% (Test Product 5)

Results

Apparatus qualification: 5 of 6 parameters were successfully validated (Table 1). Parameter 1 – the capacity of the VDC cell – was 9.77 ± 0.13 mL instead of the nominal 12 mL.

Table 1: *Examined parameters during apparatus qualification*

Apparatus qualification	Pass
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	✓

IVRT method validation: IVRT method was successfully validated for acyclovir (Table 2). Robustness test showed that temperature deviations have a higher influence on the release rates than stirring speed deviations (Figure 1 and 2).

Table 2: *Method validation results*

Method validation	Result	
Membrane inertness	Recovery of 105.5%	✓
Receptor solubility test	Acyclovir solubility > 10 times higher than the maximum acyclovir concentration in the receptor medium observed during the IVRT study	✓
Linearity	Lowest R^2 value was 0.97, no outlier	✓
Precision and reproducibility	Inter-run variability 5.8 %; intra-run variability 4.4 %	✓
Recovery	< 10%; no excessive acyclovir depletion	✓
Robustness	Release rate for temperature and stirring speed variation deviate < 15% (Figure 1 and 2)	✓

Robustness test

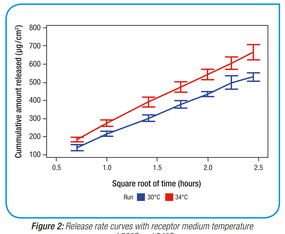


Figure 2: *Release rate curves with receptor medium temperature of 30°C and 34°C*

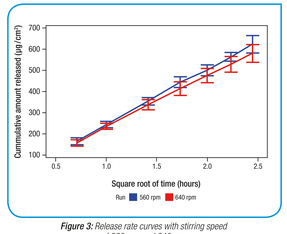


Figure 3: *Release rate curves with stirring speed of 560 rpm and 640 rpm.*

Comparative IVRT study: None of the five 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% and 133.33% (Table 3).

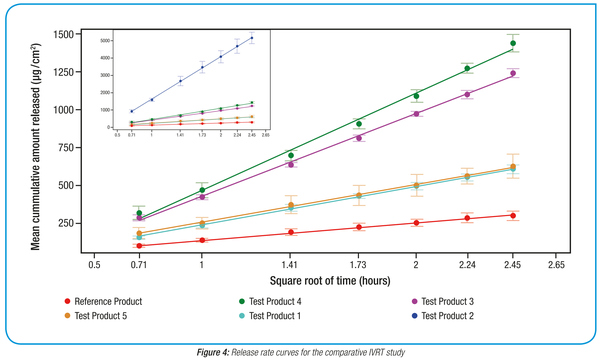


Figure 4: *Release rate curves for the comparative IVRT study*

Table 3: *Computed confidence interval for the release comparison*

Equivalence comparison	Computed confidence interval	
	Lower Limit [%]	Upper Limit [%]
Test Product 1 versus Reference Product	206.4	249.3
Test Product 2 versus Reference Product	1873.8	2402.7
Test Product 3 versus Reference Product	426.8	532.5
Test Product 4 versus Reference Product	510.2	614.1
Test Product 5 versus Reference Product	350.2	428.5

Conclusion

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

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