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DELIM

REGULATORY-COMPLIANT IVRT DEVELOPMENT FOR Q3 EQUIVALENCE OF A GENERIC TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUG EMULGEL ACCORDING TO EMA GUIDELINE EMA/CHMP/QWP/708282/2018 REV.1

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01 Introduction

As part of the development of a generic semisolid topical emulgel containing a non-steroidal anti-inflammatory drug (NSAID), an *in-vitro* release testing (IVRT) method was developed in accordance with Annex 1 of EMA Guideline EMA/CHMP/QWP/708282/2018 Rev.1. Due to the complex, multiphase nature of the emulgel formulation, IVRT was identified as a critical tool playing a pivotal role in demonstrating Q3 equivalence to the Reference Listed Drug (RLD).

02 Choice of apparatus

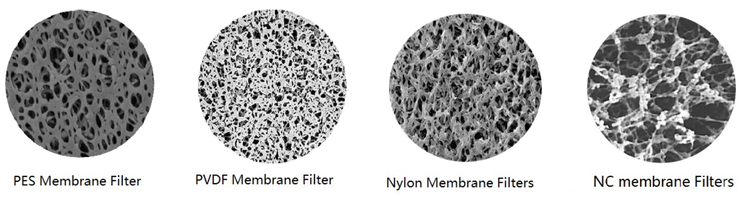
A Vertical Cell Diffusion Test System HDT 1000 (Copley) apparatus, in compliance with USP <1724>, was selected for this study. The apparatus accommodates up to 10 cells per run and is equipped with magnetic stirring (400-2000 rpm) and dry heating block system (up to 150°C). The Franz diffusion cell (Vertical Diffusion Cell 15 mm x 11 mL Type "C", Copley), used to investigate the drug *in-vitro* release profile, comprises two compartments: the donor containing the finished product and the other containing the receptor solution, separated by an artificial membrane. Diffusion cells have a diffusional area of 1.77 cm^2 and a 11.0 mL receptor compartment. The receptor chamber of each cell is equipped with a magnetic stirrer and completely filled with the medium to reach the defined mark in the sampling arm.

Vertical cell diffusion test system

03 Study design

The IVRT was developed and optimized according to EMA Guideline to compare test batches and RLDs.
To confirm the suitability of the study, IVRT has been designed in terms of:

Membrane Selection: Synthetic membranes were chosen based on their ability to separate the formulation from the receptor medium without limiting the release rate or binding the active pharmaceutical ingredient (API).
Different artificial membranes were tested: cellulose acetate/nitrate, PVDF, PES and nylon in two different pore sizes (0.2 and 0.45 µm). 0.2 µm porosity nylon membrane achieved optimal results. Its compatibility and inertness was confirmed by testing API adsorption and membrane integrity during the assay.



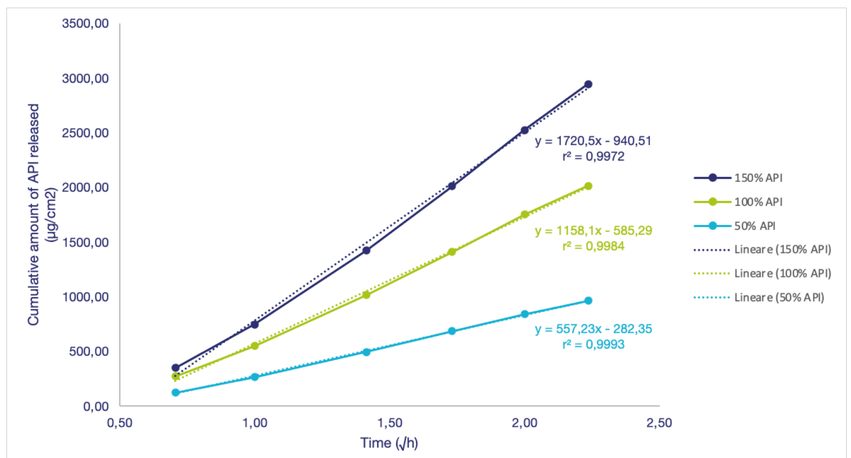
PES Membrane Filter | PVDF Membrane Filter | Nylon Membrane Filters | NC membrane Filters

Receptor Medium: The receptor medium was selected to ensure pH stability and sink conditions, with the volume at least 3 times the saturation volume of the API. pH has been determined as constant (std dev. = 0.01) throughout the experiment to prevent API degradation or precipitation. Phosphate buffer pH 7.4 has been selected as candidate.

Sampling time and experimental Conditions: Vertical Franz diffusion cells were used at controlled temperature (32 ± 1°C) to simulate skin surface conditions. Mixing speed was standardized at 600 rpm, and sampling was performed hourly to capture the linear release phase. From EMA guideline, at least 6 time points should be obtained in the linear portion of drug release profile, including the first sample immediately after drug diffusion has reached a steady state.

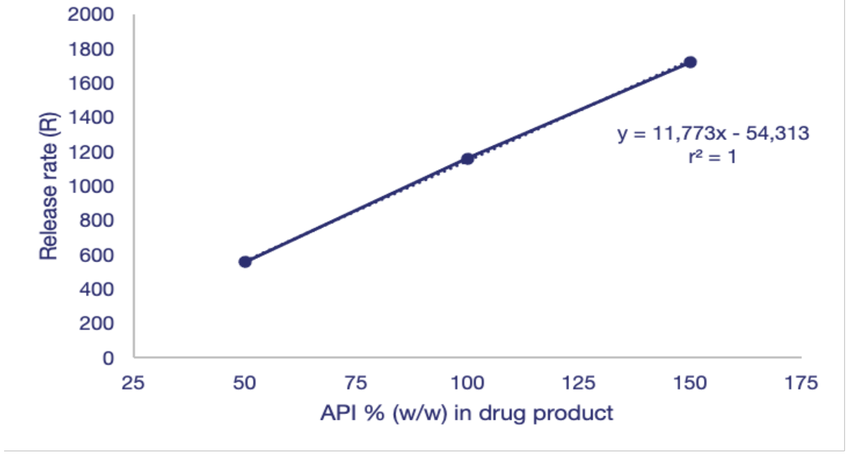
Dose and Application: A pseudo-infinite dose was applied uniformly over the membrane surface to ensure consistent and reproducible drug release. The formulation amount was validated to be within ±10% consistency across replicates, minimizing evaporation effects.

Method Validation: Discrimination was evaluated using formulations with varying API concentrations (50%, 100%, and 150% of the nominal label), confirming linearity of the release rate (R) versus drug concentration ($r^2 > 0.90$).



Release rate as a function of drug concentration in three different API strengths

From data shown, it is possible to define the developed IVRT sensitive, due to the ability to detect changes in the release rate, as a function of drug concentration in the formulation.
The IVRT method consistently detects higher or lower release rates for formulations with increased or decreased concentrations, respectively, compared to the nominal label claim concentration of the reference standard, which is tested in parallel on the same day.



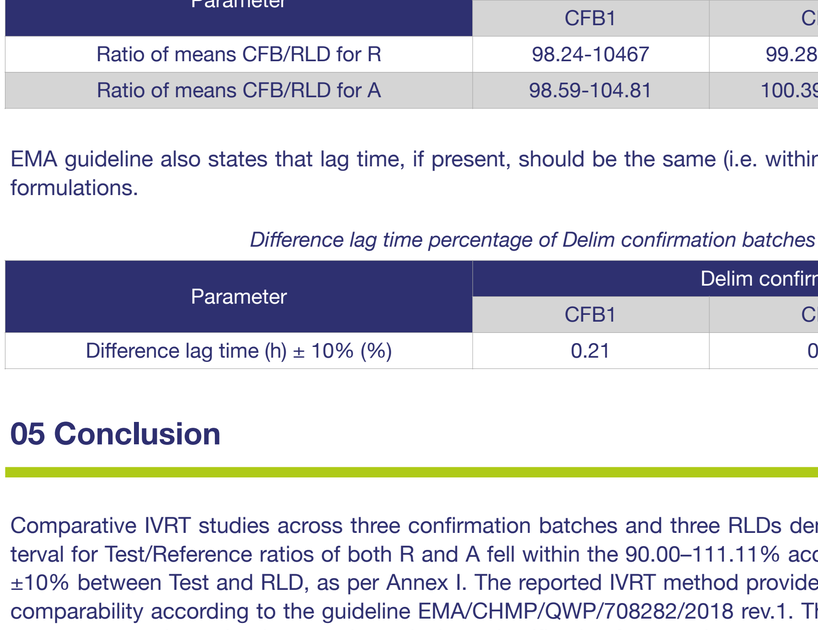
Linearity correlation of formulation concentration to rate of drug release (R)

Also, the specificity of IVRT, as ability to accurately monitor the proportionality of changes in the release rate as a function of drug concentration in the formulation, has been checked. The specificity of the IVRT method was evaluated by calculating and plotting the data with a linear trend line, and the linearity was quantified using the r^2 value. To be considered specific, the IVRT method should demonstrate a proportional linear response to differences in release rates, with a minimum r^2 value of ≥ 0.90 for the correlation between drug concentration and the average IVRT release rate (slope).

As demonstrated, the r^2 value obtained is ≥ 0,90: the IVRT method can be considered specific.

04 Confirmation batches vs Reference Listed Drugs

After having selected the most suitable membrane and the best receptor medium able to assure sink condition, API release from three RLDs and three Delim confirmation batches across nylon 0,2 µm membranes was evaluated. Each batch was tested in 12 cells replication. The data from the comparison of the API release among RLDs and confirmation batches are presented as the cumulative amount of active pharmaceutical ingredient permeated per unit area (µg/cm2) as a function of square root of time (√h). From each cumulative curve, a line equation is obtained. The slope of the equation represents the drug release rate (mg/$cm^2h^{0.5}$), parameter useful for the comparison among Test and Reference batches.



Release profile of Delim confirmation batches and RLDs

Following *EMA guideline – Annex I IVRT*, the 90% confidence interval for the ratio of means of the Test and the Reference for the drug release rate (R) and for the cumulative amount of active substance released at the last sampling time (A) of the linear portion should be contained in the acceptance interval between 90-111%. This because reference product variability is lower than 10%.

Confidence interval for the ratio of means of Delim confirmation batches versus RLDs for R and A

Parameter	Delim confirmation batches		
	CFB1	CFB2	CFB3
Ratio of means CFB/RLD for R	98.24-10467	99.28-104.78	100.65-107.13
Ratio of means CFB/RLD for A	98.59-104.81	100.39-105.22	101.97-106.73

EMA guideline also states that lag time, if present, should be the same (i.e. within ± 10%) among Test and Reference formulations.

Difference lag time percentage of Delim confirmation batches versus RLDs

Parameter	Delim confirmation batches		
	CFB1	CFB2	CFB3
Difference lag time (h) ± 10% (%)	0.21	0.85	0.43

05 Conclusion

Comparative IVRT studies across three confirmation batches and three RLDs demonstrated that 90% confidence interval for Test/Reference ratios of both R and A fell within the 90.00–111.11% acceptance range. Lag time was within ±10% between Test and RLD, as per Annex I. The reported IVRT method provided a scientifically robust basis for Q3 comparability according to the guideline EMA/CHMP/QWP/708282/2018 rev.1. This targeted, regulatory-aligned IVRT strategy strengthens the therapeutic equivalence justification for complex, non-systemically acting topical generics.

07 References

- Guideline on quality and equivalence of locally applied, locally acting cutaneous products EMA/CHMP/QWP/708282/2018;

- ICH Q2(R2) Guideline on validation of analytical procedures EMA/CHMP/ICH/82072/2006;

- Ramireddy AR, Behara DK. Formulation and optimisation of Ozenoxacin topical nano-emulgel including a comprehensive methodology to qualify and validate the critical parameters of an *in-vitro* release test method and *ex-vivo* permeation test. DOI: 10.1080/03639045.2024.2327466. April, 2024.

- Sarıbey G, Kahraman E, Güngör S. Synthetic membrane selection for in vitro release testing (IVRT): A case study of topical mometasone furoate semi-solid dosage forms. DOI: 10.1016/j.ejps.2024.106934. December, 2024.

08 Contacts

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