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Key Aspects in Developing Appropriate IVRT Method For Topical Generic Products: Advances and Challenges

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Presentation Outline

- The Rationale of In Vitro Test (IVRT); Challenges and Considerations
- Critical Aspects of Method development/validation
- Addressing Common Challenges demonstrating the IVRT methods discriminatory capabilities
- Overcome challenges of QC, Stability studies and method transfer

The Guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
CHMP/QWP/708282/2018
Committee for Medicinal Products for Human Use (CHMP)

Draft guideline on quality and equivalence of topical products

Draft Agreed by QWP	7 June 2018
Adoption by CHMP for release for consultation	18 October 2018
Start of public consultation	14 December 2018
End of consultation (deadline for comments)	30 June 2019
Agreed by QWP	
Adopted by CHMP	
Date for coming into effect	

Annexes I and II of this guideline replace Annex 1 of the Guideline on Quality of Transdermal Patches (EMA/CHMP/QWP/608924/2014)

The guideline replaces Questions and Answer on Guideline: Clinical Investigation of Corticosteroids Intended for Use on The Skin CHMP/EWP/21441/2006.

Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments: Specific recommendations are provided below.

[1] Guidance for Industry ANDA Submissions – Refuse-to-Receive Standards, Revision 1 (May 2015)

Recommended Dec 2014; Revised Dec 2016

Fundamentals of IVRT : Drug Release from Semi-Solid Matrix

International Journal of Pharmaceutics 418 (2011) 6–12

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journal homepage: www.elsevier.com/locate/ijpharm

Review

Higuchi equation: Derivation, applications, use and misuse

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Conclusions

- The classical Higuchi equation had a tremendous impact in the field of advanced drug delivery and still affects the work of numerous research groups all over the world.
- His equation allows for a very easy calculation of drug release from a rather complex type of system.
- However, caution should be paid not to violate any of the conditions the derivation of this equation is based on!

The Drafted Guidance Provides Specifics for:

- IVRT-Instrumentation
- IVRT-Method Development
- IVRT-Method Validation
- IVRT-Data Presentation
- IVRT- Documentation

IVRT-Rationale, Method Development:

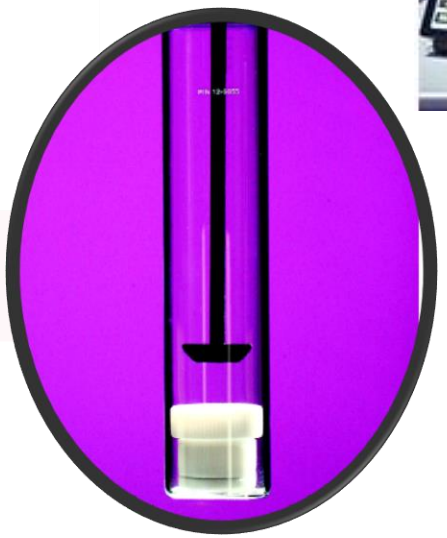
IVRT method is acceptable if during development it has met the following parameters:

- Drug release is controlled by diffusion and is not limited by the solubility of drug in a receptor medium or membrane
- Saturated solubility of a drug in the receptor medium is ~5 times greater than that of the maximum achievable concentration during an experiment
- The membrane doesn't act as a barrier, significant rate limited factor and does not interact with either applied product or receptor solution
- Diffusion coefficient of the drug remains constant, Slope-linear part of Cumulative amount API released-Q versus $(time)^{1/2}$, steady-state approach $R^2 > 0.98$
- Analytical methods sufficiently sensitive to quantify API amount at all time points and validated
- IVRT is not expected to correlate with In Vivo performance

Choice of Relevant In Vitro Diffusion System

Vertical Diffusion Cell (VDC) – Franz Cell

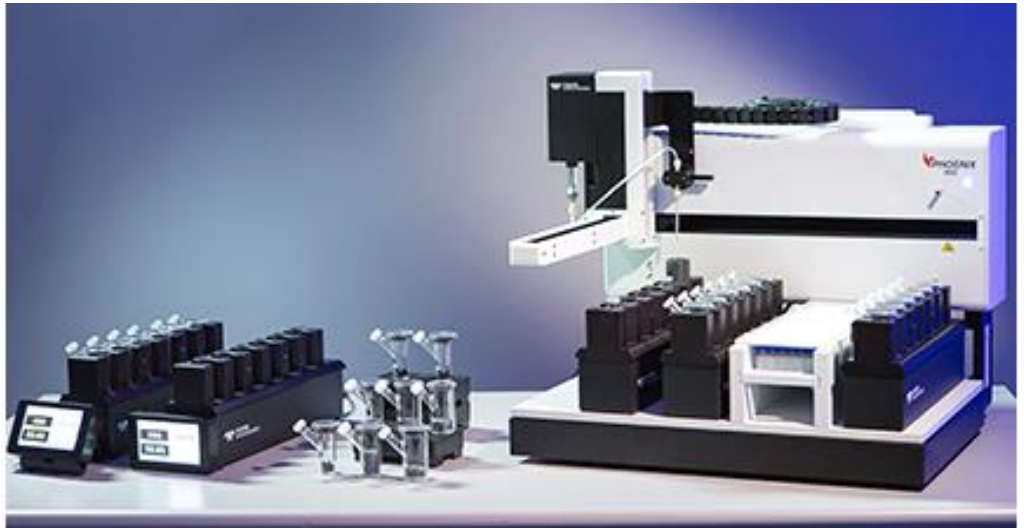
The best Choice !



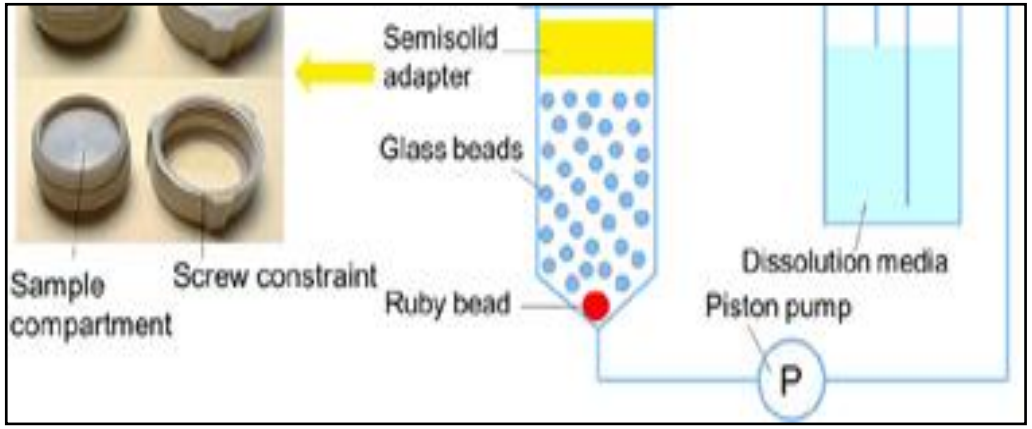
USP Apparatus 2 with Enhancer Cells

Rare cases, justification for the usage is needed

Phoenix™ Dry Heat Diffusion Testing Systems

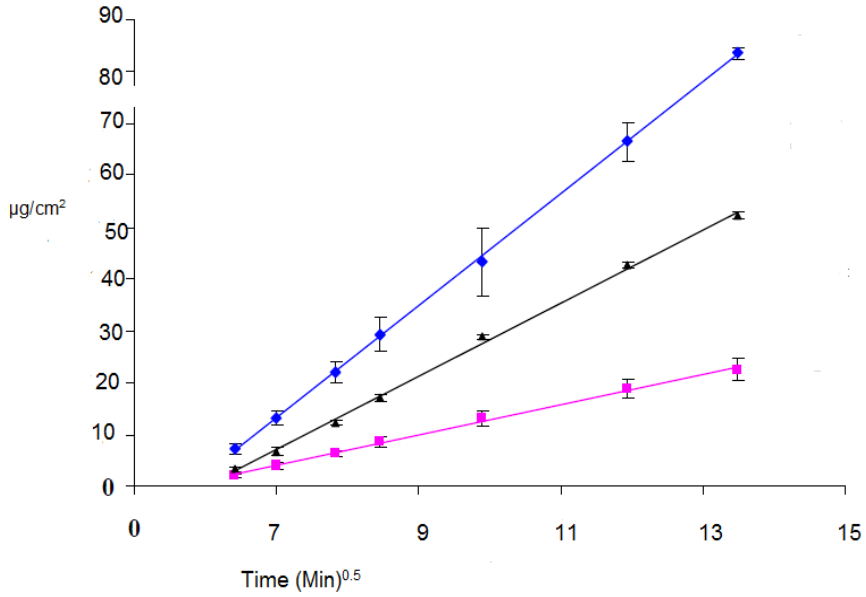


USP Apparatus 4 with the Semisolid Adapters



Selection of IVRT Conditions: Receptor medium membrane, timepoints, duration

- Ideally, receptor medium should be aqueous systems. However, for products formulated with water-insoluble drugs, could considered surfactants and organic solvents
- The solvents such as ethanol/isopropanol or propylene glycol and aqueous solutions of various concentrations are widely used for an IVRT method development
- Normally investigated 3 different receptor mediums and 3 different membranes
- Plot a linearity curve with the sample concentrations at each time point vs. the square-root of time elapsed
- The coefficient of determination (R^2) of the plotted curve should be equal to or greater than 0.95



Selection of IVRT Conditions: Receptor and Membrane

Synthetic Membranes (Recommended)

Numerous synthetic membrane pore sizes (0.25 µm and 0.45 µm) were evaluated including: mixed cellulose esters (MCE), cellulose acetate (CA Durapore® (PVDF), Millipore Express® PLUS (Polyethersulfone (PES), polytetrafluoroethylene (PTFE), and Nylon (Millipore HNWP type).

Dialysis Membrane (Rare cases, Inadvertently introduces a rate-limiting diffusion**)**

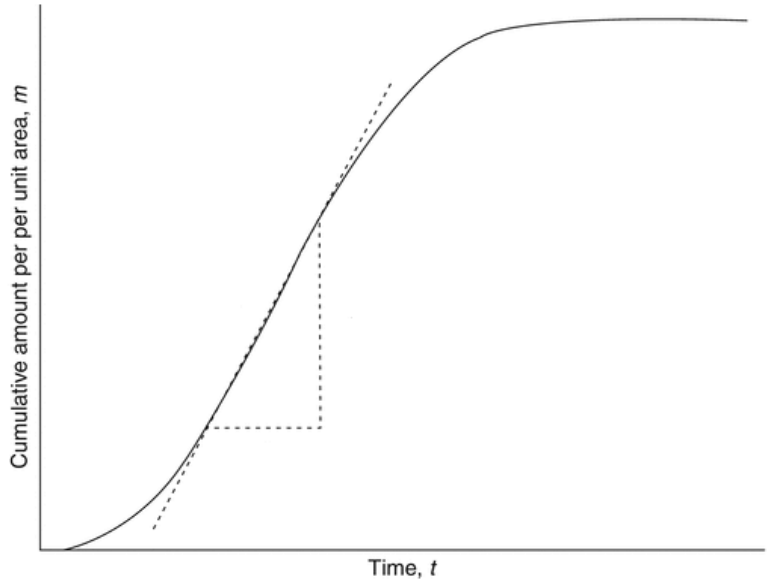
The dialysis membrane molecular weight cut-off (MWCO) was 12,400 Da or 5 – 300 kD.

Synthetic Membranes

IVRT Method Development

- In-vitro drug release-rate testing duration and sampling times may be varied depending on the formulation matrix.
- ✓ Release profiles for two formulations:
  fast-releasing PG/PEG based ointments (1) and **slow-releasing Petrolatum based ointment (2).**
- For most fast-release matrix types earlier sampling times (between zero to four hours) could be more discriminative, e.g., higher quality indicating than later time points.
- Another extreme case is the petrolatum-based ointments. Negligible to nil release of drug in many of traditional IVRT receptor solutions
- Many of hydrophilic solvents clot the matrix and after a certain timepoint stopping release a drug
- Need to use a strong organic solvent e.g., THF with the optimal mixture of polar solvents to help dissolve a drug that could be hydrophilic

Selection of IVRT Conditions: timepoints, duration



- ✓ IVRT data at least 5-timepoints (typically 6), from each 6 cells should be obtained
- ✓ IVRT duration -The best linearity curve fitting -at least 4 hrs (typically 6hrs)

IVRT Method Development: Sample application and collection

❑ Pseudo-Infinite dosing is preferable to evaluate rate of API release from semi-solid drug products

- ✓ Dose Amount control, reproducibility (± 5% EMA)
- ✓ Uniformity dosage, avoid bubble creation
- ✓ qualification method of product application and sample volume collection
- ✓ Starting time must be staggered and synchronized with sampling time for each successive diffusion cells

Sample occlusion

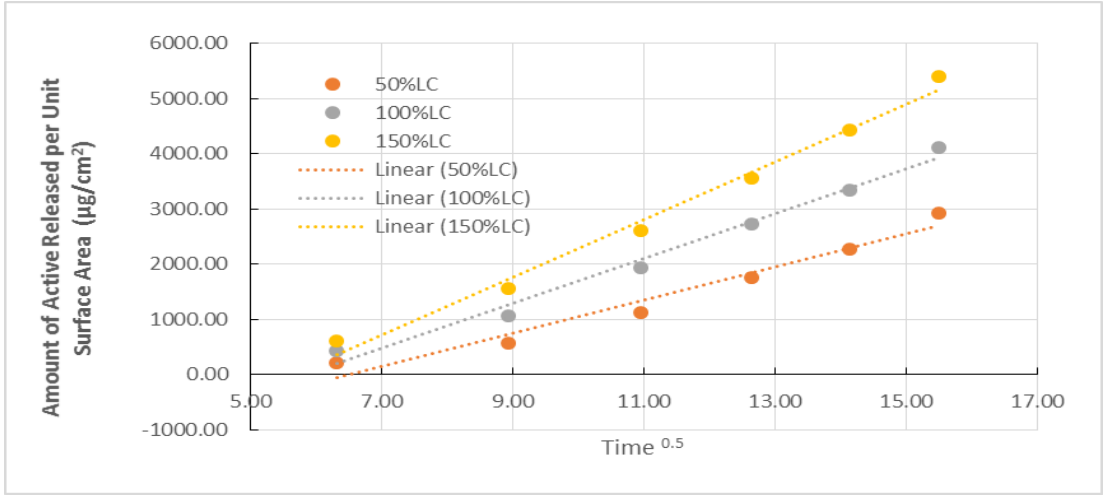
- The FDA guidance recommends keeping cells occluded, no formulation evaporation or leak

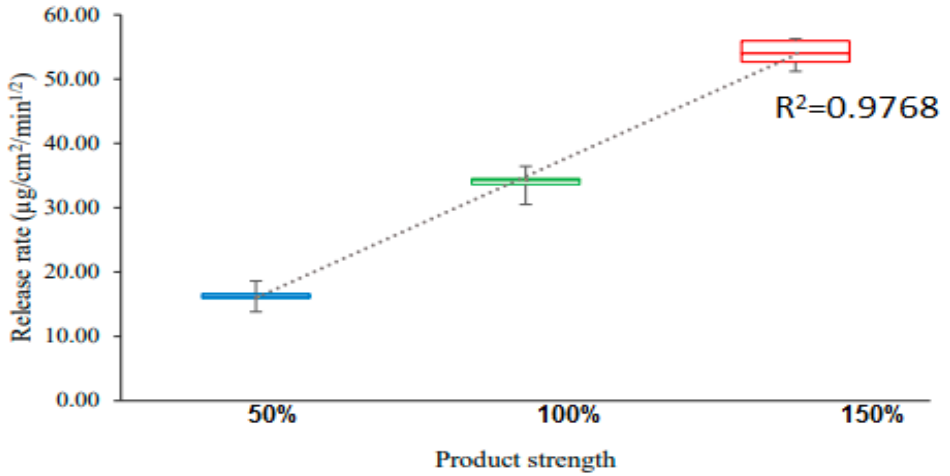
In Vitro Release Test (IVRT) Validation

Validation Components

- Linearity and Range
- Accuracy/Precision and Reproducibility
- Mass Balance
- Sensitivity and Specificity
- Selectivity
- Robustness
- Membrane Inertness
- Receptor Solution Solubility/Stability

Average Cumulative Release(µg/area(cm^2) vs. square root of time ($min^{0,5}$)

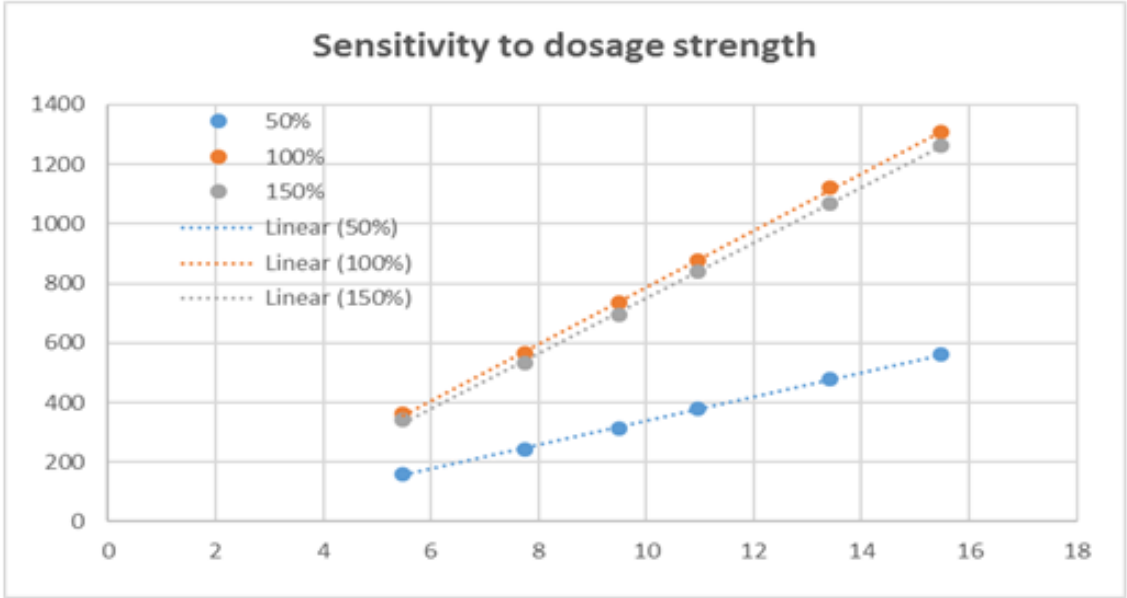




In Vitro Release Test (IVRT), Discriminatory Power

Case Study #1

- Failure IVRT lots comparison test to demonstrate method's discriminatory power on 100%LC vs 150% LC
- In such cases one plausible suggestion could be to prepare series of altered lots 50%LC, 75%LC, 100%LC, and 125%LC and demonstrate trends of increase/decrease slopes as a function of API concentration



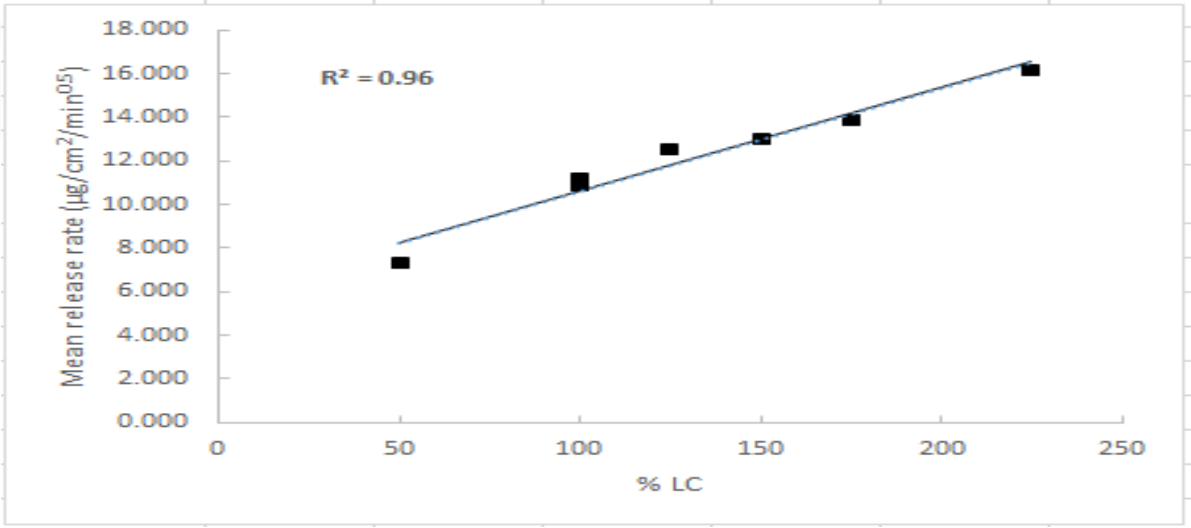
- Perhaps the CI, EMA proposed, limiting the confidence interval to 90–110%, instead of the 75–133% CI, could be used (?)
- however, this restrictive CI might compromise acceptance of lots of comparison tests during pivotal study (?)

In Vitro Release Test (IVRT), Discriminatory Power

- Some products with slow and well-controlled release matrixes at the increased level of API concentration might not be necessary demonstrates the proportionality in release rate increases i.e. twice increases the concentration in 100%LC would not always results of double slope but increases is less than 2 in many cases following like squire root of two (double increases in concentration show only 1,4 increases in slope.

Specificity (mean release rate vs % LC)

% LC	Mean release rate ($\mu g/cm^2/min^{0.5}$)
50	7.312
100	**10.847**
100	**11.192**
125	12.491
150	13.014
175	13.878
225	16.159



In Vitro Release Test (IVRT), Discriminatory Power

Release Rate Comparison

	100%:	**Reference**							
	225%:	**Altered**							
			100%-1	100%-2	100%-3	100%-1	100%-2	100%-3	
		Slope	**11.859**	**11.497**	**11.741**	**11.639**	**10.456**	**12.741**	
	225%-1	**16.268**	1.3718	1.4150	1.3856	1.3977	1.5559	1.2768	
	225%-2	**15.717**	1.3253	1.3671	1.3386	1.3504	1.5032	1.2336	
	225%-3	**16.431**	1.3855	1.4292	1.3995	1.4117	1.5714	1.2896	
	225%-1	**15.897**	1.3405	1.3827	1.3540	1.3658	1.5204	1.2477	
	225%-2	**16.213**	1.3671	1.4102	1.3809	1.3930	1.5506	1.2725	
	225%-3	**16.431**	1.3855	1.4292	1.3995	1.4117	1.5714	1.2896	

Note: Rank 36 T/R ratios from lowest to highest, the eighth and twenty-ninth ordered ratios represent lower and upper limits of the 90% CI for the ratios of release rates.

Eighth Ordered Ratio:	**133.86%**
Twenty-Ninth Ordered Ratio:	**142.92%**
Criteria:	**100% and 150% LC are considered to be the "same" if the 90% CI falls within the limits of 75% - 133.33%.**
Conclusion:	**Sameness not confirmed**

- suggestion : make series of altered lots with the API concentrations at varies of levels E.G 50%, 75% 100% 125%, 150%, 175% etc. and demonstrate the trend where lots with low API contents are displaced the low release rate and lots with high APIs are with higher slopes and importantly, this variability must be larger than the method reproducibility (inter-intra days precisions)
- Apparently, there is a need for alternative statistical approaches that could be applied to identify the significant differences among the lots. Certainly, the selected models should have enough discriminatory power and distinguish changes made in composition or/and manufacturing process

In Vitro Release Test (IVRT), Discriminatory Power

Case # 3

- In this very rare case, API in the formulation is acting as a viscosity builder. Consequently, the changes made in the amount of API will inevitably affect the rheology of the product. The viscosity of altered lots with 50%LC and 150%LC are very different from the reference product. Subsequently, the release rates did not adequately respond to the changes made in the amounts of API. The adjustment of the viscosity within Q1/Q2 equivalency is the challenging

Two plausible solutions:

- Introduce the additional viscosity adjustment ingredients in the formulation if regulatory agency agreed)
- The altered lots made by variation in the amounts of inactive ingredients.
- Method well responded to the changes made in the amount of inactive ingredients (supplemental selectivity)

IVRT in stability testing program and method transfer

a) One additional challenge is the inclusion of the IVRT as shelf life, stability testing program of the topical product.

- It is necessary to consider the inherent IVRT method variability. The sources of IVRT variability may be caused by a complex of factors, such as air bubble entrapment during product application.
- Bubbles between membrane and product could be created due to back diffusion
- Difficulty to reproduce the exact amount of formulation loaded in the system (e.g.±5% as per EMA)
- Semisolid products metamorphosis
- Therefore, in many cases, regardless of an IVRT method successfully has been validated within ±15 % of slope variability but during a routine basis stability testing program could observe larger inconsistency of the release rate.
- In order to propose practical applicability of IVRT for the stability program it is critical to establish more realistic criteria for each individual product

b) Until now there is no guidance for an IVRT method transfer

- It is crucial for release rate reproducibility that both sides have the same diffusion system, preferably automated (the same manufacture) to reproduce the diffusion parameters, cell dimension, volume, mixing rate, etc.
- Three products in three days: a) negative control (altered formulation), b) positive control (RLD) and Testing (exhibit) formulations

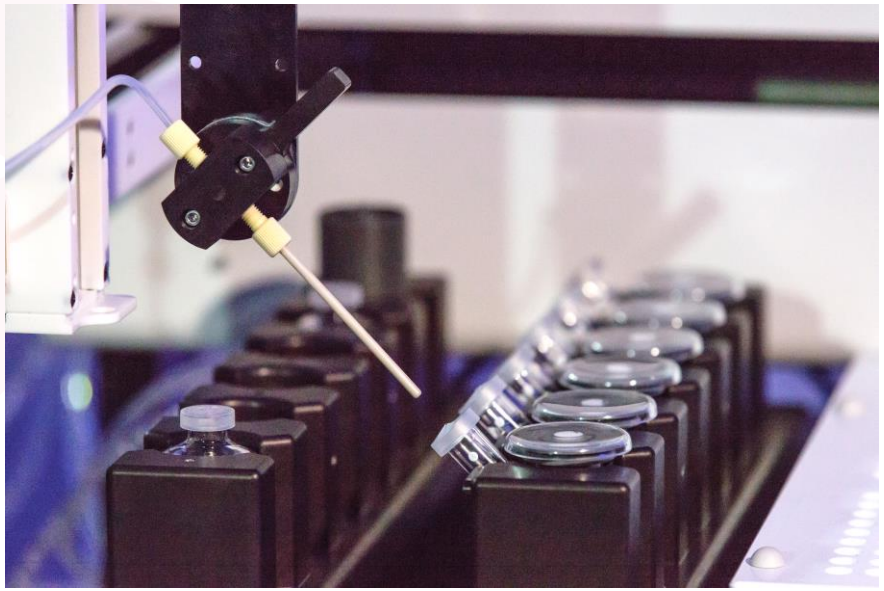
IVRT Summary and Conclusions

- The determination of the in vitro release profile is useful in many scenarios. It can provide essential data on the product's microstructure (Q3) during product development, valuable to optimize both formulation and production process..
- During late-stage development, as well as post-marketing phase, as a quality control tool to monitor batch-to-batch consistency as well as product shelf-life program
- The main advantages of this method rely on its high sensitivity and discriminatory power, which are often able to reflect the physicochemical differences of topical semisolid drug products.
- Moreover, in specific conditions, in vitro release testing can be used to demonstrate the products bioequivalence when compared to a pre-approved product.
- Traditionally use vertical diffusion (‘Franz’) cells, this testing is now being automated to improve throughput and reproducibility

About Diteba Laboratories

IVRT and IVPT Expertise

We specialize in method development and validation of release-rate studies and percutaneous absorption studies for topical creams, lotions, ointments, gels, pastes, less viscous solutions, suspensions, and transdermal patches for product development and regulatory purposes.



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Thank You

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