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Bioequivalence Considerations for In Vitro Release Test Methods of Ophthalmic Products

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Outline

General Bioequivalence (BE) approach for ophthalmic products

Ophthalmic products with In Vitro Release Test (IVRT) recommendation

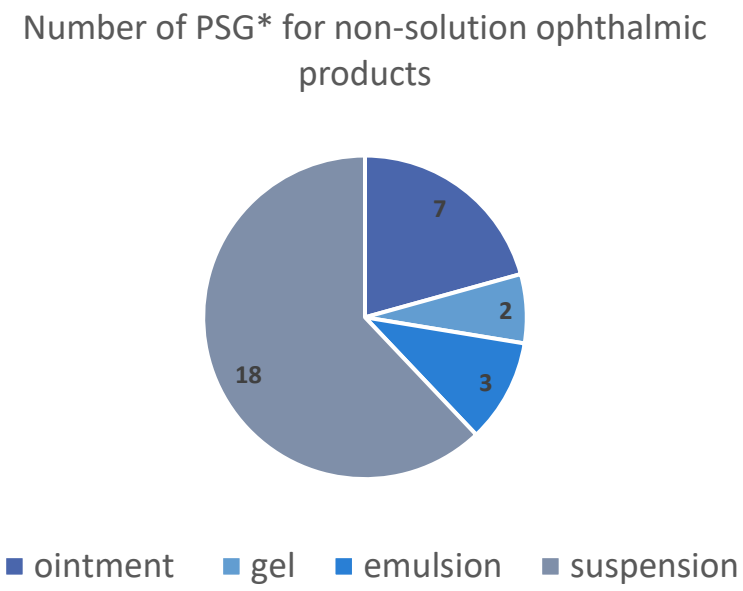
Key Parameters of IVRT method

- IVRT method development
- IVRT method validation
- Pivotal IVRT Study

Common BE deficiencies/considerations on IVRT methods

Take Home Message

Product-Specific Guidance (PSG) Recommendations for Ophthalmic Products



* Multiple PSGs are available for one drug product due to different reference products.

- General PSG Recommendations
  - In Vitro Option:
    - qualitatively (Q1), quantitively (Q2) same formulation and comparable physicochemical properties (Q3) with IVRT
  - In Vivo Option:
    - In vivo clinical endpoint study or
    - In vivo pharmacokinetic (PK) endpoint study in aqueous humor
- Some Exceptions in PSG
  - In vivo BE study only: Latanoprost ophthalmic emulsion & Brinzolamide ophthalmic suspension etc.
  - In vitro study only: Loteprednol Etabonate Ophthalmic Suspension (0.2%) & Tobramycin Ophthalmic Ointment etc.
    - If not Q1/Q2, an appropriate in vivo BE study should be submitted

Roles of IVRT

- IVRT for bioequivalence determination is one component of a totality of evidence approach
  - Part of in vitro testing to demonstrate sameness of drug products
  - Evaluation of comparable delivery of drug product
- IVRT can also be used as a specification to control product quality and/or acceptability of post-approval manufacturing changes

Ophthalmic products with IVRT recommendation

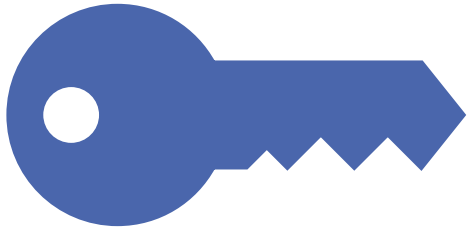
Dosage Form	Drug Product	RLD	Approved using in vitro option (April 2022)
Suspension/Drops	Besifloxacin Hydrochloride	022308	
	Dexamethasone; Neomycin sulfate; Polymyxin B sulfate	050023	
	Dexamethasone; Tobramycin	050818/050592	2
	Fluorometholone	016851/019216	
	Fluorometholone Acetate	019079	
	Loteprednol Etabonate	020583/020803	2
	Loteprednol Etabonate; Tobramycin	050804	
	Nepafenac	021862/203491	
	Prednisolone Acetate	017011	
Emulsion	Cyclosporine	050790	1
	Difluprednate	022212	2
Gel	Loteprednol Etabonate	202872/208219	1
Ointment	Ciprofloxacin HCl	020639	
	Loteprednol Etabonate	200738	
	Tobramycin	050555	
	Acyclovir	202408	

PSG Recommendation for IVRT methods

- *Acceptable comparative in vitro drug release of Active Pharmaceutical Ingredient (API) from the test and Reference Standard (RS) formulations.*
- *The methodology used for in vitro drug release testing should be able to discriminate the effect of process variability in the production of the test formulation.*
- *Detailed information on development and validation of a proposed in vitro drug release testing method should be provided.*

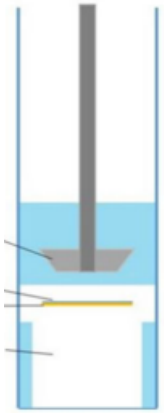
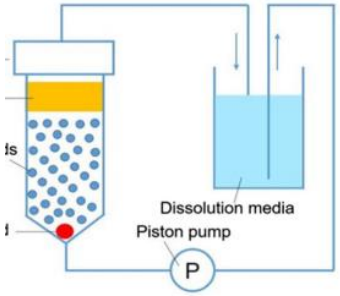
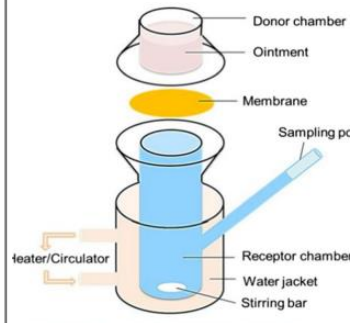
- No compendial method/general guidance: Fit-for-purpose IVRT methods.
- IVRT methods should be accurate, precise, sensitive, and selective to ensure equivalence in drug release between the test and reference products.
- When used as part of totality of evidence approach, no need to mimic physiological conditions or performance.

Key parameters of IVRT methods used for ophthalmic products



Method Development

Apparatus/Adaptor Selection

Apparatus	USP Apparatus II (Paddle)	USP Apparatus IV (Flow-Through Cell)	Vertical Diffusion cells	Rotating Bottle
Sample holder (Adaptor)	Dialysis Membrane	Dialysis Membrane	Membrane	Dialysis Membrane
	Immersion Cell	Membrane (filter)		
	Suspension Cup	Semi-solid adaptor		
				

Graphical illustrations were adapted from Pharm Res (2018), 35, 234

Method Development: Other parameters

Parameters	Considerations
Membrane	separation of samples from media, comparability, no diffusional resistance, pore size
Receptor Solution	solubility, stability, pH, temperature,
Dose application	optimization of dosing amount
Sampling time points	complete release

Method Validation

Reproducibility

- Precise (e.g., low % CV)
- Robustness against minor disturbance
  - examples
    - Flow rate
    - Temperature
    - Sample loading amount
    - Dissolution medium concentrations
    - pH of dissolution media
    - Media volume

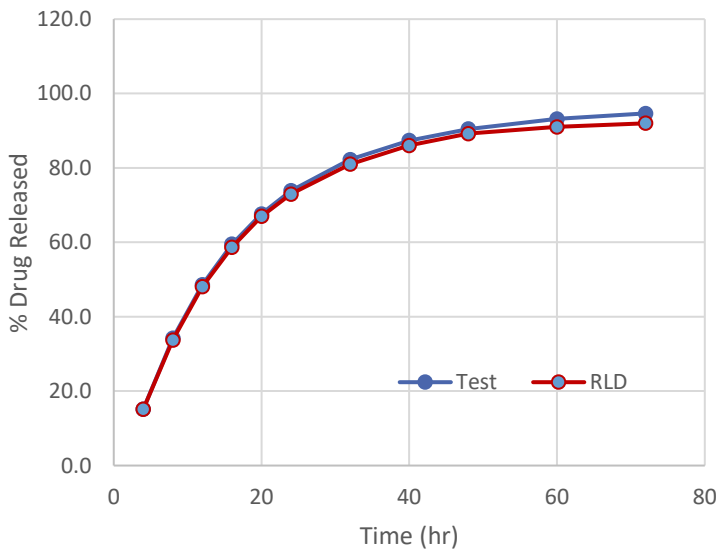
Discriminatory ability

- IVRT method should be able to discriminate non-bioequivalent batches
- Sensitivity using different API amount
- Specificity using non-bioequivalence batches with process variability in the production of the test formulation.
  - Changes in particle size
  - Changes of excipients

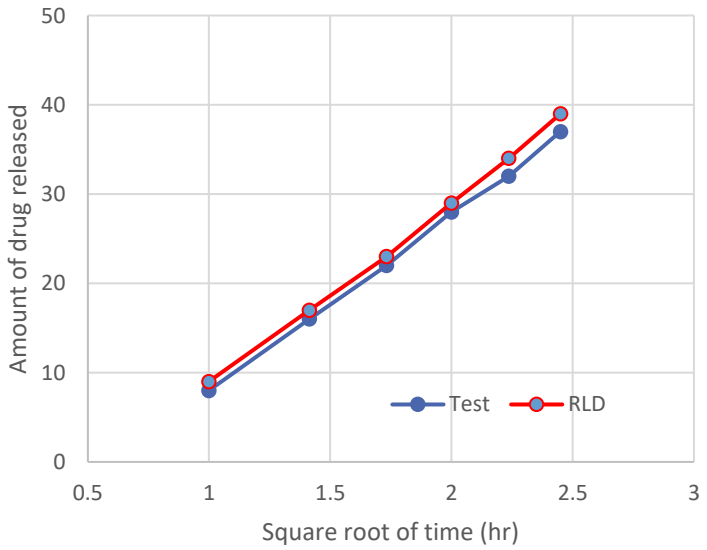
Pivotal IVRT Study

- Complete and comparable release: reach a plateau and achieve at least 80% release
- Statistical evaluation (e.g., similarity factor f2 approach)

ANDA-A: Acceptable



ANDA-B: Not acceptable



ANDA: Abbreviated New Drug Application

Common Deficiencies: Missing Documents

- Reports: IVRT method development, IVRT method validation, analytical method validation, and pivotal IVRT study
- Raw data: analytical raw data matching with each part of study
- Batch Information: All drug products including altered formulations
  - Manufacturing date, manufacturing process change, batch size, potency, and content uniformity, etc.
- Standard Operating Procedure: All SOPs listed in the study report
- Protocols: method validation and pivotal IVRT study

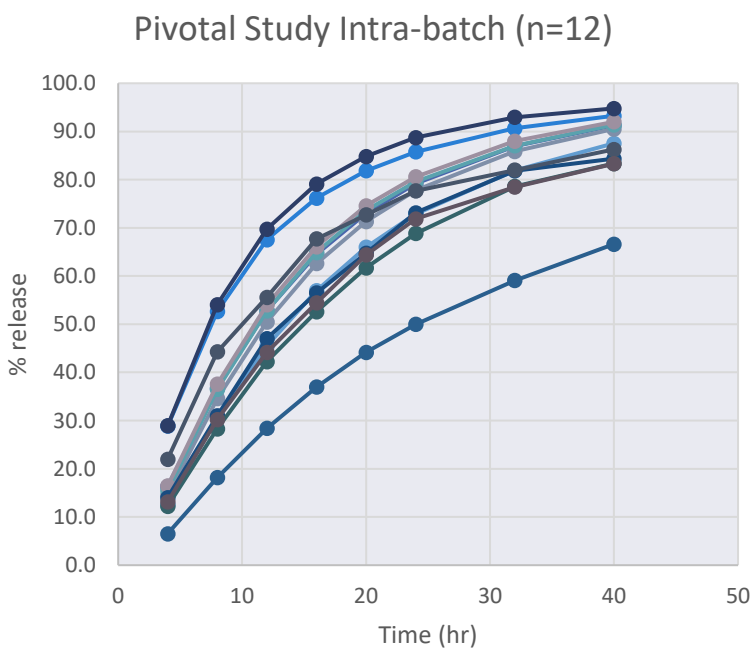
Common Deficiencies: Missing Information and Justification

- Method development stage: Lacking supporting evidences to optimize method
  - Choice of specific membrane/dialyzer
  - Pore size of membrane
  - Selection of release medium
  - Temperature
  - pH of media
- Method validation stage: incomplete validation
  - Solubility and stability method
  - Mass balance
  - Precision and robustness
  - Discrimination
  - Analytical method validation

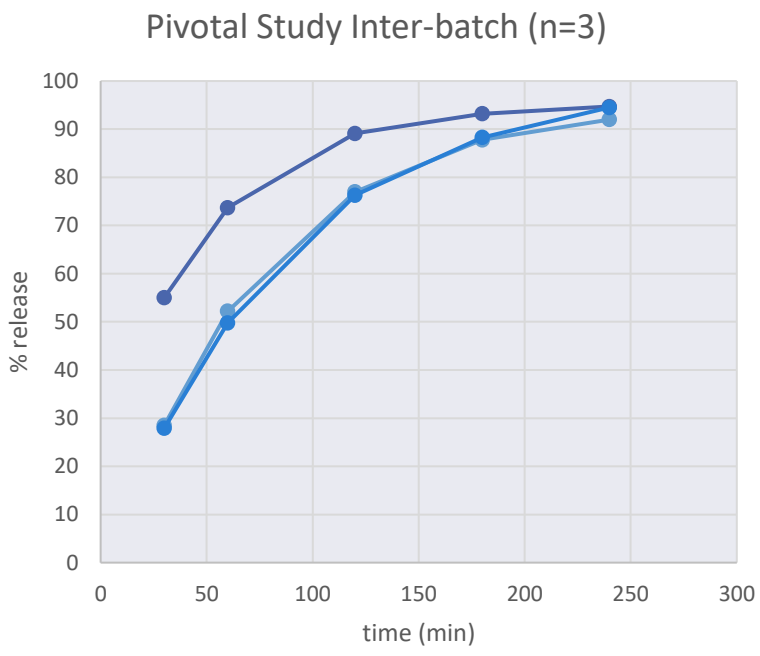
Common Deficiency

High Variability

Intra-Batch

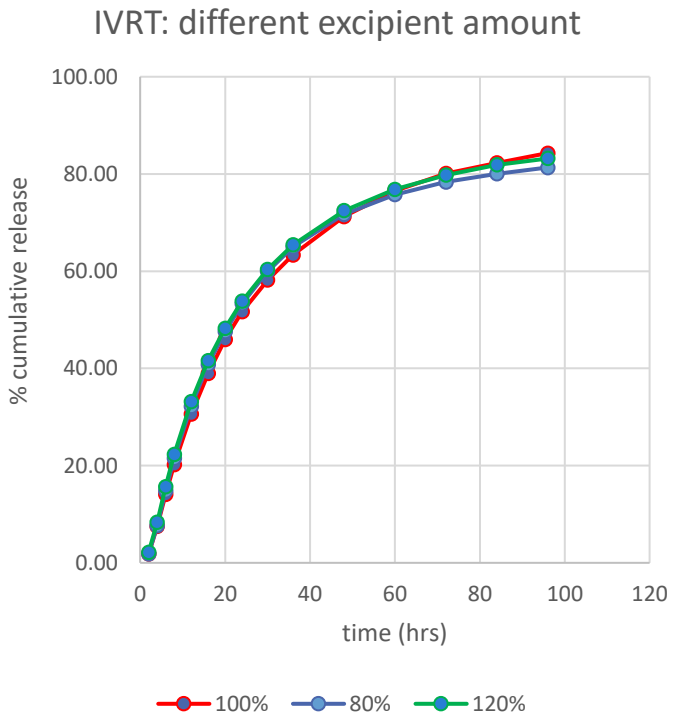


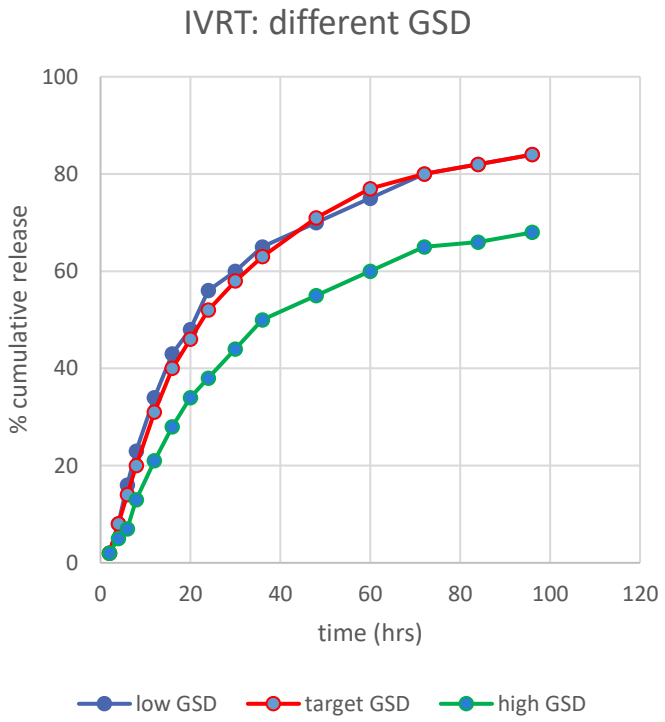
Inter-Batch



Common Deficiency

Discrimination

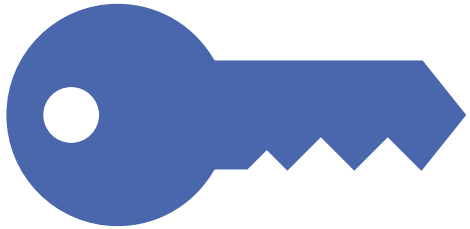




- In case IVRT method cannot discriminate the certain changes, **justification should be provided**.

GSD: Globule Size Distribution

Key Considerations of IVRT method in different ophthalmic dosage forms



Emulsion Products

- Membrane selection and Mass balance
  - The proposed IVRT method is measuring drug release from the formulation rather than the transfer of formulation/oil droplets across the membrane.
- Complete and comparable release
  - Reach a plateau and achieve at least 80% release
- IVRT Statistical Analysis
  - The evaluation method of drug release data using semisolid transdermal drug product is not applicable to an ophthalmic emulsion product (i.e., Durezol® or Restasis®) considering different release mechanism from receding boundary and emulsion globule.
  - Release profiles are compared using the f2 similarity factor.

Suspension Products

- Discrimination
  - Particle size of ophthalmic suspension is an important consideration in terms of irritation and ophthalmic bioavailability. Therefore, discrimination with different particle size are recommended.
  - Process parameters

    e.g. homogenization changes
  - Excipient changes
- High variability
  - Sample loading amount/method

Gel Products

- IVRT Method Discrimination
  - Particle size distribution and viscosity of ophthalmic gel are the key parameters. Therefore, discrimination with different particle size and viscosity levels are recommended.
  - Other changes such as pH, osmolality, and excipients can be considered to support IVRT method discriminative power.

Take Home Message

Understanding the purpose of IVRT method for bioequivalence

- Confirmation that a proposed generic product has a comparable release rate to that of the reference listed drug (RLD) to ensure that the proposed generic product will deliver drug in a same manner to that of the RLD.
- Reproducible and discriminative method.

Understanding your ophthalmic products

- Release mechanism and factors controlling drug release should be considered.
- Drug product-specific IVRT method is recommended.
- Various IVRT methods have been used for determining drug release from ophthalmic products.

Good quality of study reports

Acknowledgement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