Common Deficiencies-OGD Considerations

Complex Generic Drug Product Development Workshop

How to resolve current challenges in ANDAs for topical products

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- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Product Specific Guidances: Semisolid Topical Products

- Acyclovir Ointment, Silver Sulfadiazine Cream and Docosanol Cream : Q1/Q2/Q3 + **IVRT**
- Acyclovir Cream: Q1/Q2/Q3 + **IVRT** + **IVPT**
- Benzyl Alcohol Lotion: Q1/Q2/Q3 + **IVRT** + Lice Assay
- Dapsone Gel and Ivermectin Cream : Q1/Q2/Q3 + **IVRT** + **IVPT**+ In-Vivo pK BE Study

In Vitro Release Test (IVRT)

Conducting an IVRT:

As described in the United States Pharmacopeia (USP) General Chapter <1724>, Semisolid Drug Products – Performance Tests.

IVRT

What should be submitted for evaluation?

- IVRT Method Development Report
- IVRT Method Validation Report
- Analytical Method validation Report
- IVRT Pivotal Study Report
- Standard Operating Procedure (SOP)

IVRT Method Development

Method Parameters:

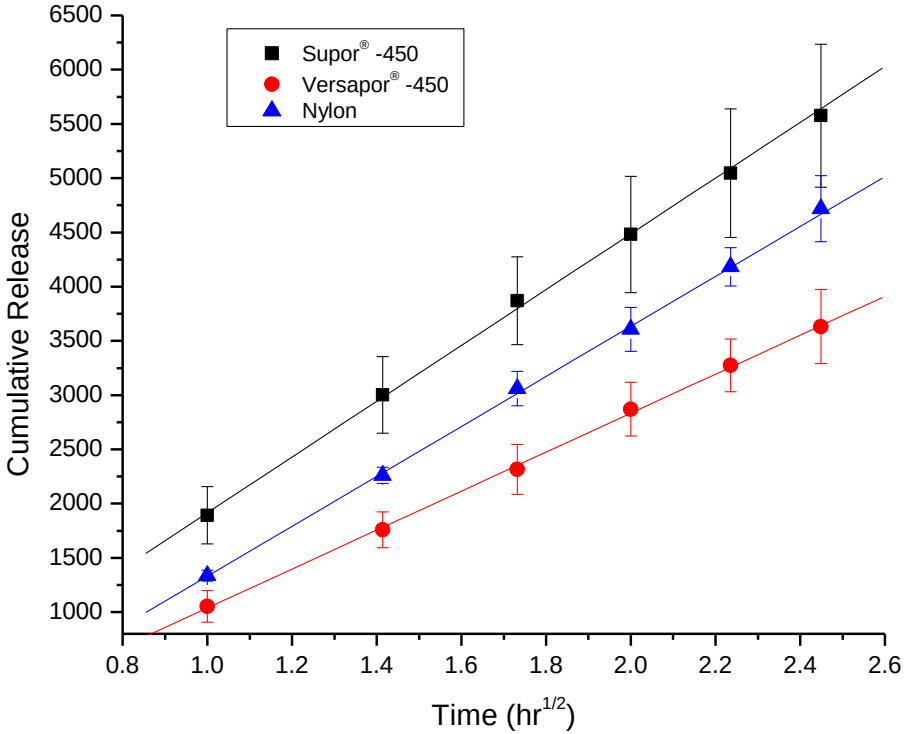
Product dose amount, Stirring rate, Sampling times, IVRT apparatus

Membrane: Inertness

Receptor Solution: Solubility and stability

IVRT Method Development

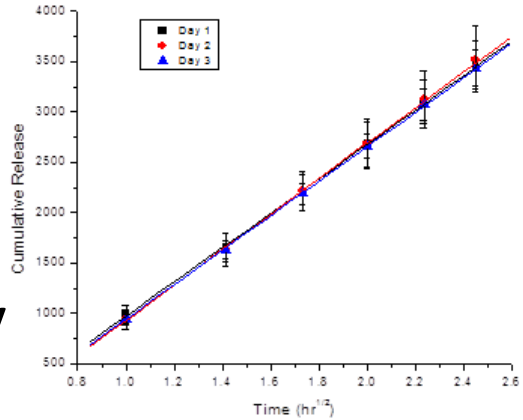
Membrane Evaluation



IVRT Method Validation

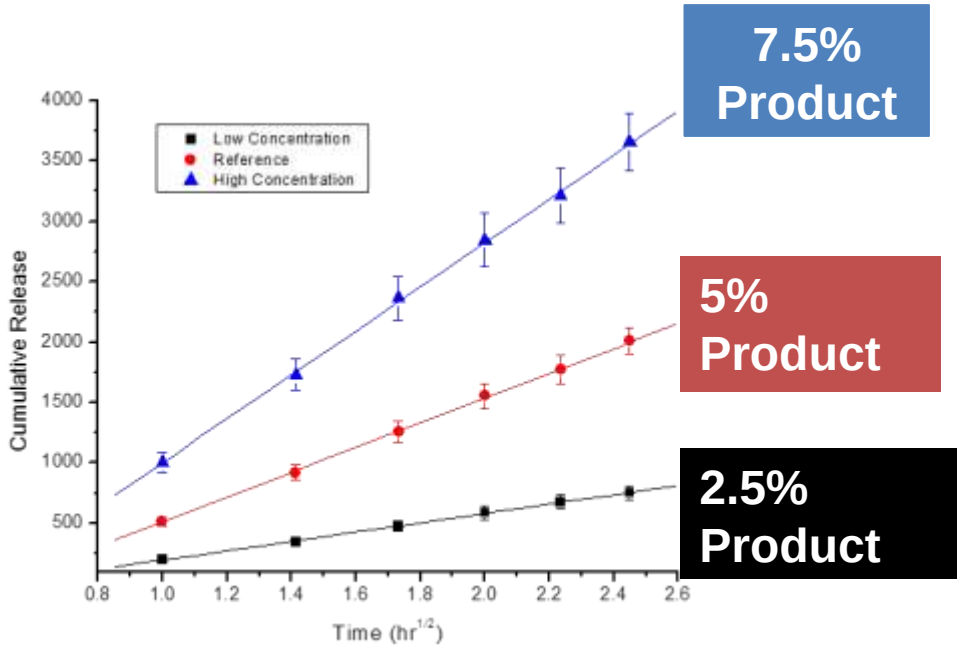
Validation Components

- Linearity and Range
- Accuracy/Precision and Reproducibility
- Recovery, Mass Balance & Dose Depletion

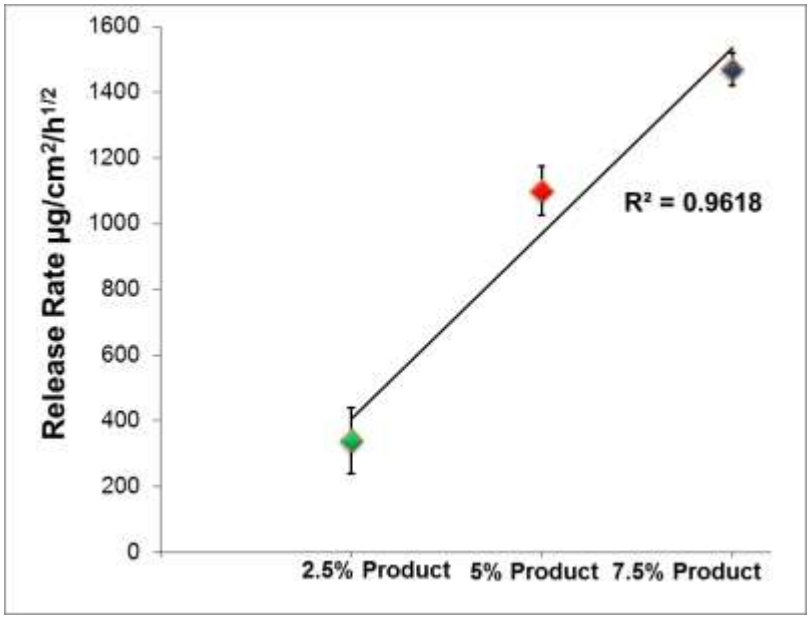


IVRT Method Validation

Sensitivity and selectivity



Specificity (Proportionality)



IVRT Method Validation

Validation Components

- Robustness
- Membrane Inertness
- Receptor Solution Solubility
- Apparatus Qualification

Deficiencies for IVRT studies

Experimental Details:

- Stir speed
- Membrane pre-soak time
- Degassing of the receptor medium
- Sample withdrawal
- Amount of sample loaded (dose per cell)

Deficiencies for IVRT studies

Data Analysis:

- Report on data analysis
- Raw numerical data : Dilution factor, calibration standards, and quality control samples
- IVRT data in SAS Transport format

Deficiencies for IVRT studies

Incomplete Study Reports : Analytical and IVRT

- Method development reports
- Method validation reports
- Standard Operating Procedure (SOP)

In Vitro Permeation Test (IVPT)

Conducting an IVPT:

Using excised human skin mounted on a qualified diffusion cell system.

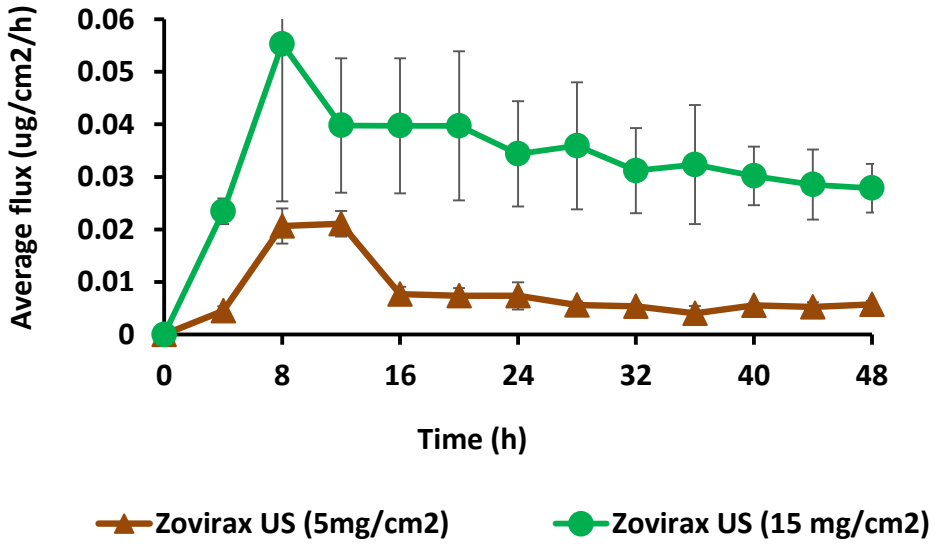
IVPT

What should be submitted for evaluation?

- IVPT Method Development Report
- IVPT Method Validation Report
- Analytical Method validation Report
- IVPT Pilot Study Report
- IVPT Pivotal Study Report
- Standard Operating Procedure (SOP)

IVPT Method Development

Method Parameters: *Product dose amount, Stirring rate, Sampling times*



IVPT Method Validation

Validation Components

- Membrane (skin) qualification
- Receptor Solution Qualification
- Receptor Solution Sampling Qualification
- Receptor Solution Sample Analytical Method Validation
- Environmental Control

IVPT Method Validation

Validation Components

- Permeation Profile and Range
- Precision and Reproducibility
- Recovery, Mass Balance & Dose Depletion
- Discrimination Sensitivity and Selectivity
- Robustness

IVPT Pilot Study

- To estimate number of donors required for the pivotal study.
- Multiple skin donors: minimum of 4 replicate skin sections per donor per treatment group.
- Parallel assessment should be performed with a third product.
- Results: should not be combined with the IVPT pivotal study.

IVPT Pivotal Study

- Non-dosed control skin section from each donor
- Pre-dose zero sample from each diffusion cells
- Duration of an IVPT study: maximum flux and a decline in the flux
- Dose staggering and sampling synchronization

Deficiencies for IVPT studies

Study Design:

- No control skin section (non dosed)
- Insufficient sampling times
- Skin from only single donor
- Skin donor Inclusion/Exclusion criteria not submitted
- Randomization sequence not submitted
- No rationale for clinically irrelevant dose

Deficiencies for IVPT studies

Experimental Details:

- Temperature
- Size of the tissue mounted on the Franz diffusion cell
- Skin conditions (occluded vs unoccluded)
- Speed of rotation (stir bar)
- Dosing and sampling design

Deficiencies for IVPT studies

Data Analysis:

- Skin sections
- Raw numerical data : Dilution factor, calibration standards, and quality control samples
- IVPT data in SAS Transport format

Deficiencies for IVPT studies

Incomplete Study Reports : Analytical and IVPT

- Method development reports
- Method validation reports
- Standard Operating Procedure (SOP)

Summary

- IVRT/IVPT data reviewed by Division of Bioequivalence.
- The method validation should be performed using validated sample analytical procedures under principles of GLP.
- Inadequate submission of the data may often lead to the delay in the review process and the final approval of the application.

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