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In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods

Best Practices, Regulatory Standards and Scientific Considerations for ANDA Submissions

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Considerations in Development, Validation and Transfer of In Vitro Release Methods

Acknowledgment

- All the experimental data that will be presented were generated at either Analytical Solutions or Tergus Pharma.

Development of Robust IVRT Methods

- Selection of Receiving Medium
  - Solubility and Stability of API, Compatibility with the formulation matrix and discriminatory power
- Selection of filter membrane
  - Compatibility with the API and the formulation components, lack of binding, lack of analytical interference
- Selection of Apparatus, Sampling Times and Dose amount
  - Right choice of parameters allow managing sink conditions and infinite dose model
- Selection of Dosing technique
  - Important to make sure there in no extra shear applied to dosage form as a result of application to the apparatus

Differences in IVRT Parameters for Same Generic Product

	Product 1	**Product 2**	**Product 3**	**Product 4**	**Product 5**
Receiving Medium	0.1 N HCl	pH 7 Phosphate Buffer	70:30 1N HCL: IPA	80:20 1N HCL:IPA	75:25 1N HCl:IPA
Membrane	Supor-450 Pall	PVDF Sterlitech	PVDF Sterlitech	Tuffryn	Strelitech Nylon
Nominal Cell Volume	8 ml	12 ml	8 ml	8 ml	8 ml
Surface area of Exposure	0.999 cm^2	1.767 cm^2	1.00 cm^2	1.00 cm^2	1.00 cm^2
Method of Dosing	Syringe Application	By spreading on membrane	Syringe Application	Syringe Application	Syringe Application
Amount Dosed	1 G	400 mg	1.5 G	1.5 G	1.5 G

Challenges in Developing a Reliable IVRT method

- Hydrophobic petrolatum-based ointments present a substantial challenge to developing reproducible IVRT methods with sufficient release of drug substance. Typically, the release is not only very low, but there is no increment with time providing flat profile (parallel to the x-axis).
- Drug substance in suspension adds an additional challenge. Difficulty in achieving steady state and variability associated with soluble/insoluble ratio
- Subjectivity in implementation of dosing technique, especially when using syringe technique and when shear applied during dosing has a significant effect on the release rate.

Approaches to overcome Challenges in Development of IVRT Methods

- Extended-release time frames (> 24 hours) to allow greater release
- Surfactant-based receptor fluids
- High ionic strength receptor fluids
- Stronger solvent systems than typical hydro-alcoholic mixtures
- Membrane soaking with IPM or other solvents
- Membranes with greater pore sizes
- Increased temperatures in the receiving chambers

Hydrophilic API, Soluble in HCl and NaOH, Formulated in a Hydrophobic Ointment

Receiving Media	Membrane/Temperature	Duration
IPA:0.1N HCl (50:50 v/v) + 0.5% Tween 80	PVDF/32 °C	5 hours
ACN:0.1N HCl (50:50 v/v) + 0.5% Tween 80		
IPA:0.1N NaOH (40:60 v/v) + 2% Tween 80		
0.1N NaOH + 2% Tween 80		
DMSO:0.1N HCl (20:80 v/v)		
DMSO: ACN: 0.1N HCl (10: 40: 50 v/v)		
50:50 v/v 28.9% Sodium Lauryl Sulfate Solution: 0.1N HCl	Tuffryn/32 °C	23 hours
50:50 v/v 29% Sodium Lauryl Sulfate Solution: 0.1N HCl Membranes soaked in octanol for 10 mins	Tuffryn/37 °C	23 hours
50:50 v/v Diluent (1:4 v/v Glacial Acetic Acid: Water): 30% w/v Sodium Lauryl Sulfate Solution Membranes Soaked in Octanol for 20 mins	Glass Fiber/37 °C	24 hours
50:50 v/v 11.7% Sodium Chloride Solution: 0.1N HCl	Tuffryn/32 °C	23 hours

Challenges/Approaches in Developing a Reliable IVRT method

- Difficulty in achieving specificity and sensitivity when high concentration of API is not possible due to solubility limitations
  - Sensitivity at limited range of concentration of API-
- Lack of dependency of release rate on physical parameters such as viscosity or composition may not allow method to be specific.
  - Evaluate different dosage form

Factors Contributing to Changes in Release of Active Ingredient from Matrix

1.Particle size of API

2.pH of API

3. Incorporation of API in semisolid matrix

4. Solubility of API in semisolid matrix

1. Viscosity

2. Spread ability

3. Overall pH

4. Moisture content of dosage form

1. Presence of emollients and penetration enhancers

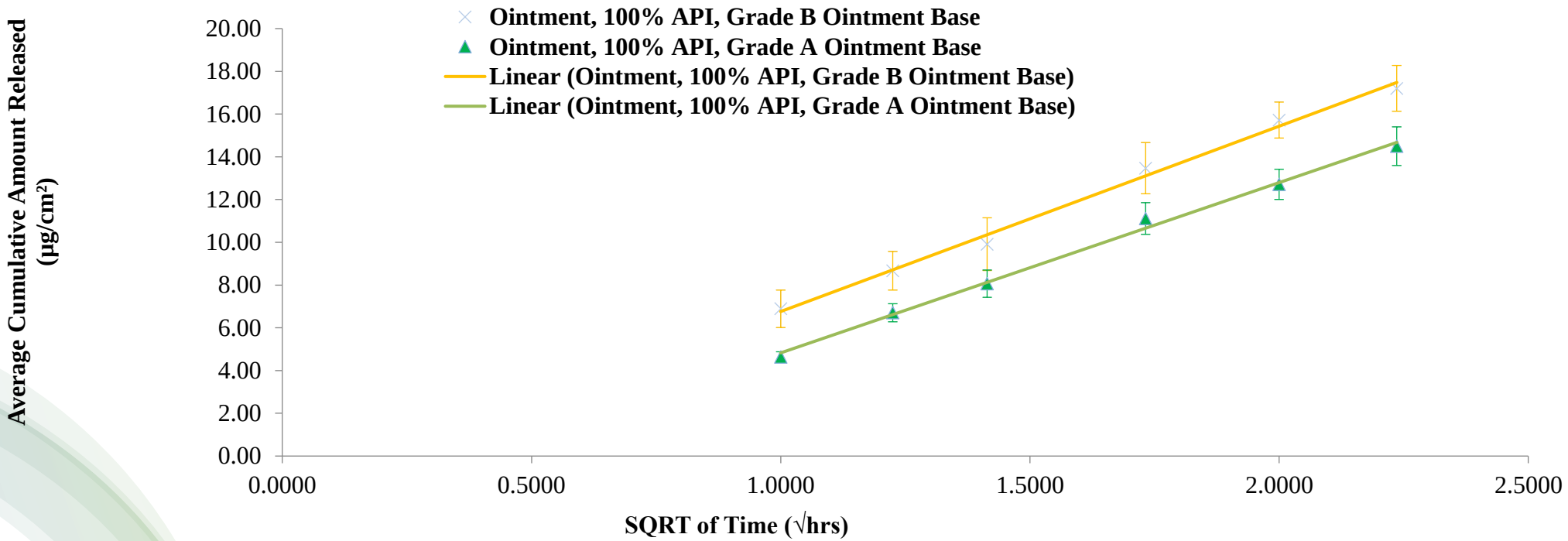
2. Effect of excipients on release of API from matrix

3. Compatibility of excipients with API and with environmental agents such as moisture, gases, to affect the release of API

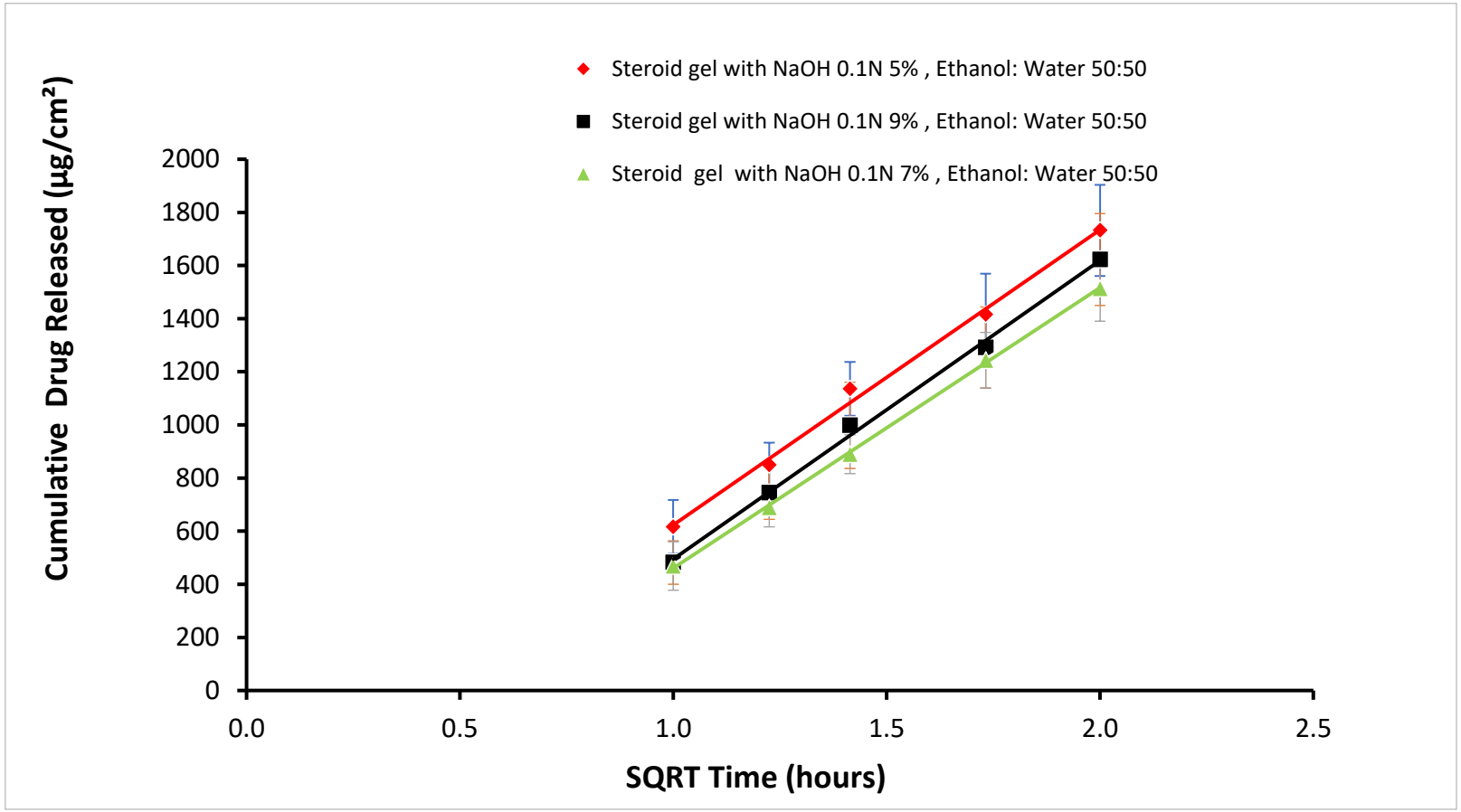
4. Manufacturing process

5. Manufacturing site

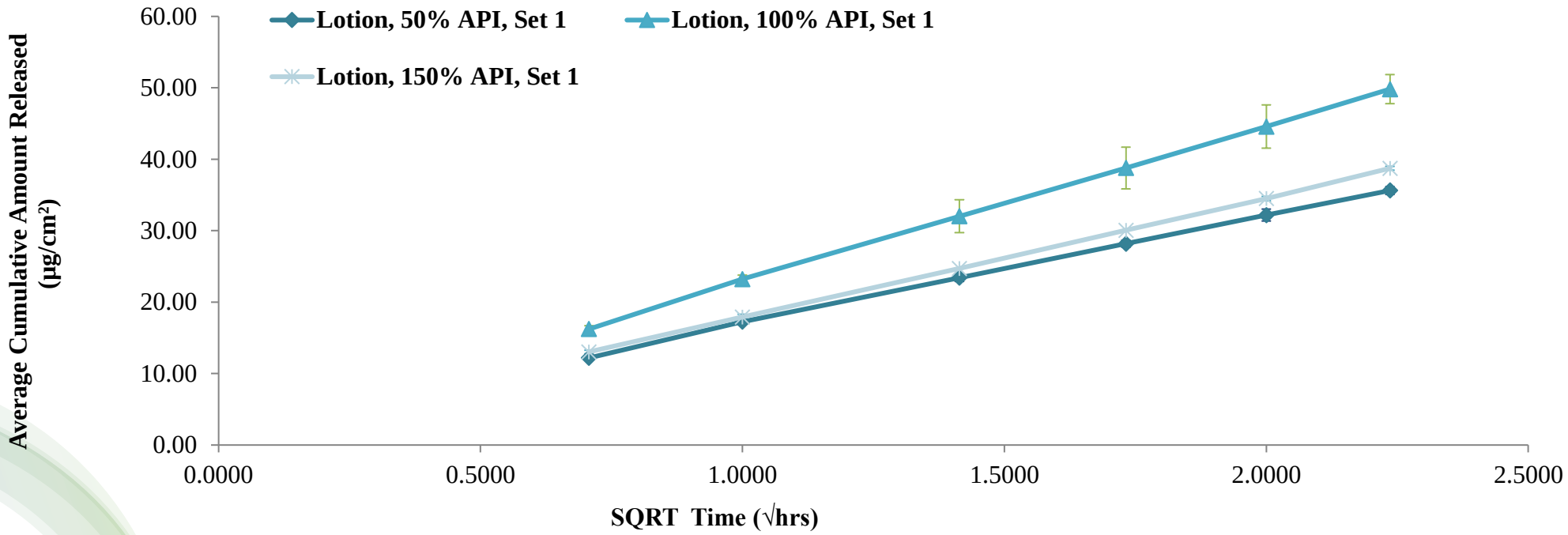
Effect of API Grade on Release Rate



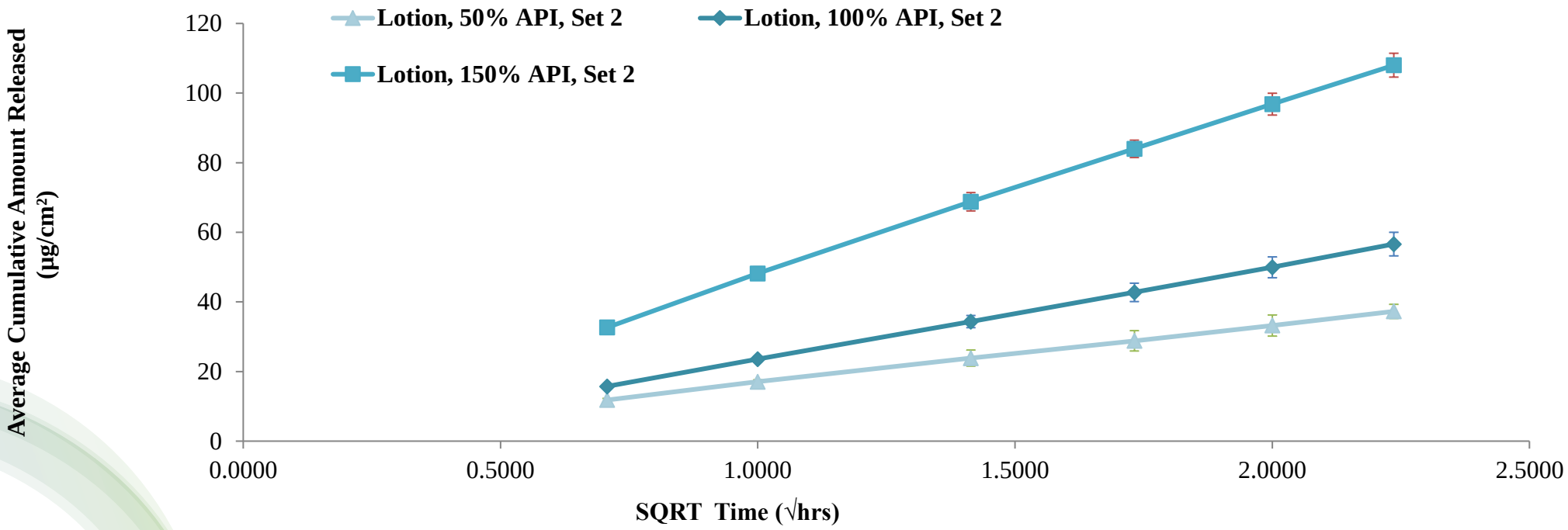
Effect of Concentration of Sodium Hydroxide on Release rate



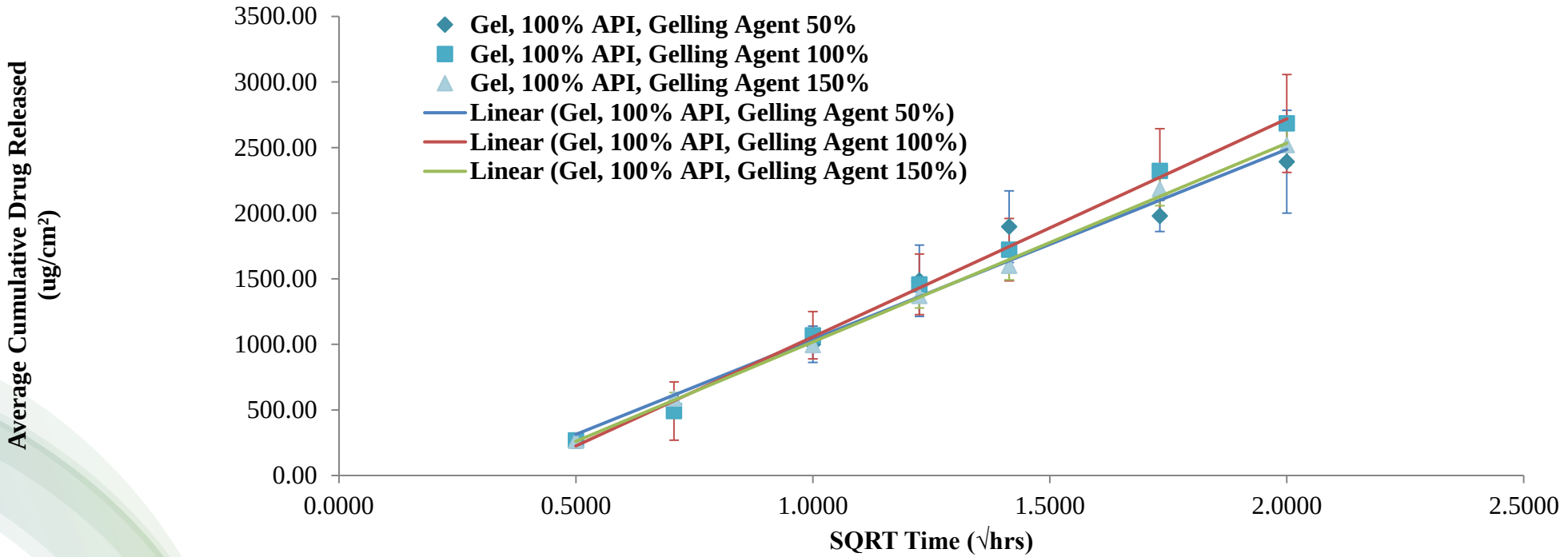
Effect of Foaming Agent on Release Rate



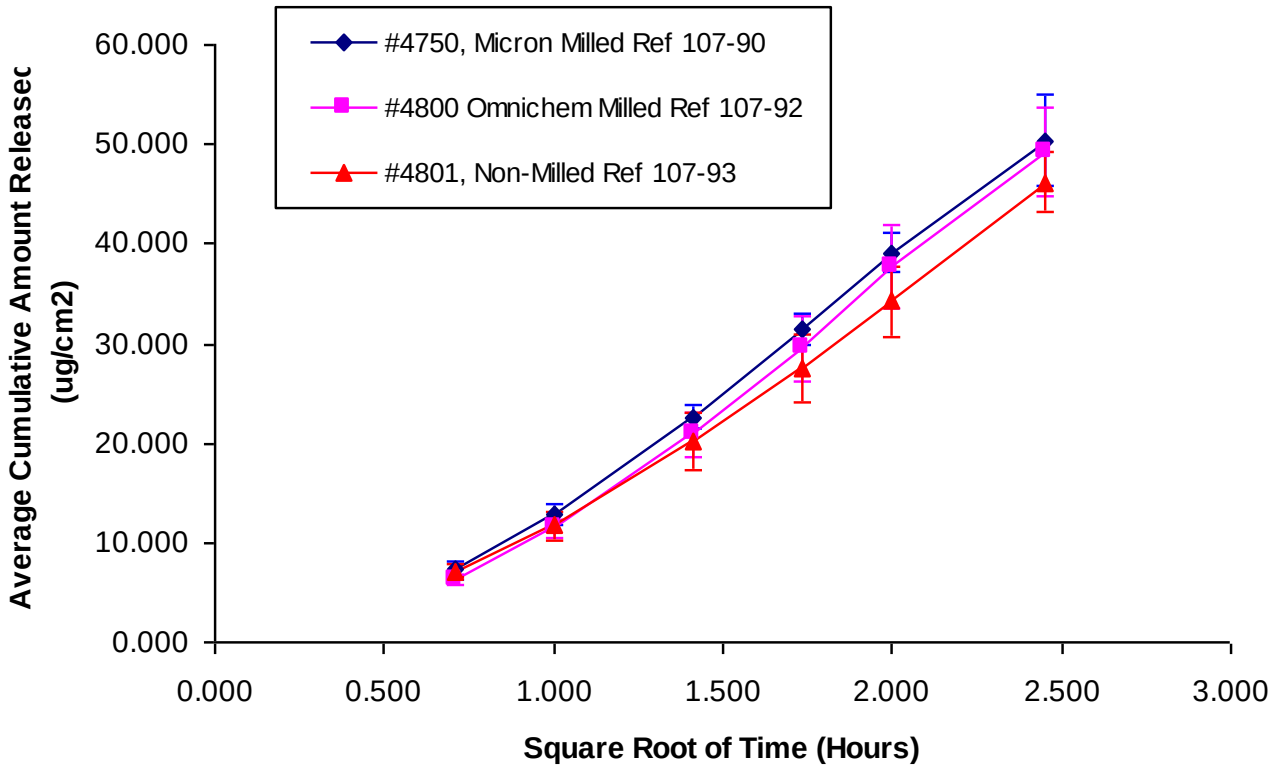
Effect of Foaming Agent on Release Rate



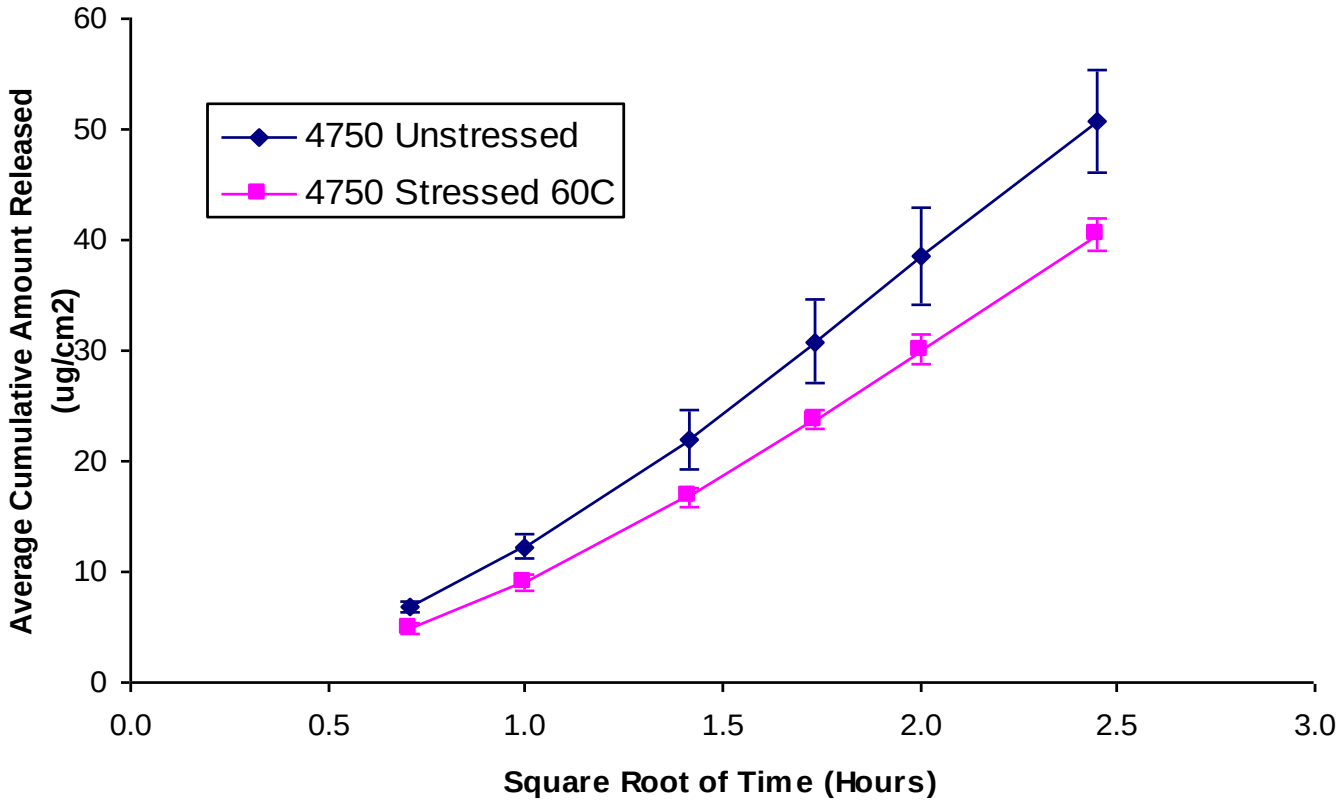
Effect of Gelling Agent Concentration on Release Rate



Effect of particle size on Release Rate



Effect of Stress Induced Viscosity Change on Release Rate



Validation of IVRT Method: Attributes to be Validated

- Precision
- Intermediate Precision
  - Day-to-Day & Analyst-to-Analyst
- Sensitivity, Specificity and Selectivity
  - Demonstrate both increased and decreased release rates with changes in dosage strength, altered formulation to demonstrate specificity
- Robustness-IVRT
  - Receptor fluid changes
  - Membrane supplier/type
  - Stirring rate
  - Cell temperature
- Robustness-HPLC
  - Mobile Phase composition
  - Flow Rate
  - Detection Wavelength
  - Injection Volume
- Solubility, Membrane Binding, Dose Depletion

Challenges in Validation of IVRT Method

- Precision: %RSD of slopes for six cells between 2-15% is acceptable.
  - Technique dependent operation. Three techniques generally used are: spreading with spatula, application with a syringe and use of transfer tubes. Improper spreading technique can introduce bubbles within formulation, syringe will introduce variable shear to formulation depending upon operator. Application with transfer tubes is relatively new and shows a lot of promise. Inconsistencies in all techniques will cause variability and loss of precision.
  - Dosage form inhomogeneity will lead to loss of precision
- Intermediate Precision:
  - Differences in techniques between operators lead to variability and loss of intermediate precision
  - Differences in environmental conditions will lead to loss of precision where release rates are highly sensitive to temperature /environment

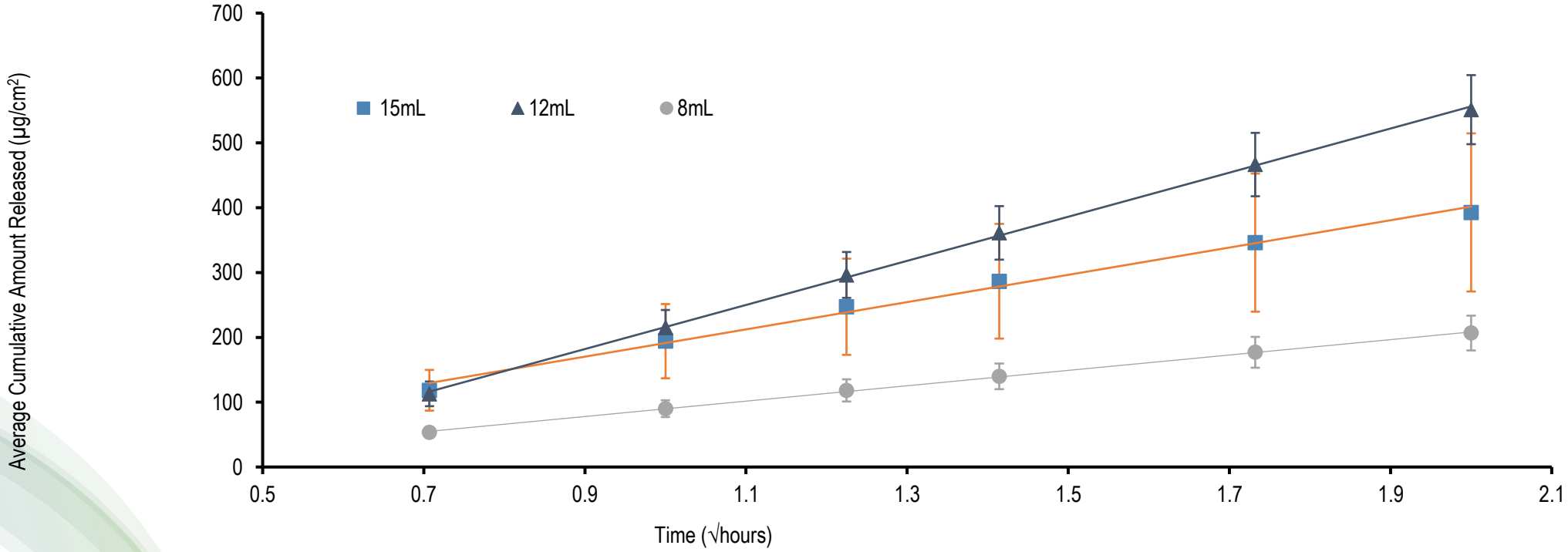
Challenges in Validation of IVRT Method

- Sensitivity, Specificity and Selectivity
  - Properly developed IVRT method can be validated with little difficulty with respect to sensitivity, specificity and selectivity
- Robustness IVRT
  - Most important parameters for robustness evaluation are the receiving medium composition and membrane.
  - When using mixed solvents, composition and preparation should be consistent. Often release rates are very sensitive to exact composition of the receiving medium. Volumetric measurements are desirable
  - For same type of membrane, different suppliers have different basic composition which can lead to differences in release profiles.

Transfer of IVRT Methods

- Considerations for Successful Transfer of IVRT Methods:
  - Type of Apparatus
    - Volume of receiving chamber
    - Surface area of exposure
    - Geometry of donor and receiving chambers
    - Sampling arm position
    - Stirring mechanism
  - Dosing Technique
    - Type of syringe
    - Application of dosage form onto the membrane
  - Occlusion Technique

Hydrocortisone Release from Hydrocortisone Cream : Different Cell Volumes



Approaches for Successful Transfer

Training:

- Transferring Facility to train the personnel at the facility where the method is to be transferred on the PVT standard and then the drug product

Transfer:

- Two 6-cell IVRT runs of the same lot of product to be conducted at both facilities within the same week.

Comparison:

- Compare the data sets from two facilities using statistical method. Wilcoxon Sum-Mann Whitney ??

Criteria:

- Method is successfully transferred when the two data sets are equivalent

thank you
danke
謝謝
ngiyabonga
teşekkür ederim
рахмат
Баярлалаа
спасибо
gracias
tapadh leat
хвала
asante
manana
mochchakkeram
go raibh maith agat
bedankt
dziękuję
hvala
maururu
obrigado
sukriya
kop khun krap
grazie
arigatō
takk
dakujem
мерси
merci
terima kasih
ευχαριστώ
감사합니다
ありがとう
dank je
sagolun
taiku
enkosi
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