

# Laboratory Science to Support Risk-Based Quality Assessments

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# OTR's Proactive Science and Research Approach



- The **science program** is designed to maintain preparedness.
  - Consumer complaints
  - Public health issues
- The **research program** is “forward looking.”
  - New and emerging technologies
  - Advanced analytics (instrument and modelling)
  - Complex Drugs

# OTR's Role in Generic Drug Science



- Laboratory consults
  - Method evaluation (verification)
  - Product Quality
  - Pharmaceutical Equivalence
- Guidance and Standard development
  - Provide laboratory Data
  - Develop improved testing protocols
- Training
  - Provide training to quality assessment staff

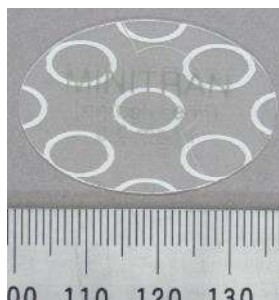
# Outline of Case Studies

- Consumer Complaints: Quality Issues in Transdermal Systems
- Public Health: Drug Delivery in Enteral Feeding Tubes
- Emerging Tools: Particle Profiling in Nasal Spray Drugs
- Improved Testing Methods: Effects of Contraction on Drug Release

# Transdermal Delivery Systems



- Different shapes
- Release liner same size as TDS or larger than TDS



# TDS-Release Liner Studies

- Release liner test measures the force required to peel
- OTR Consults for Consumer complaints :
  - Patch won't peel cleanly
  - Medication is sticking to the plastic
- OTR Consults for Quality Assessment:
  - Interlaminar adhesion studies
  - Comparison between brand and generic

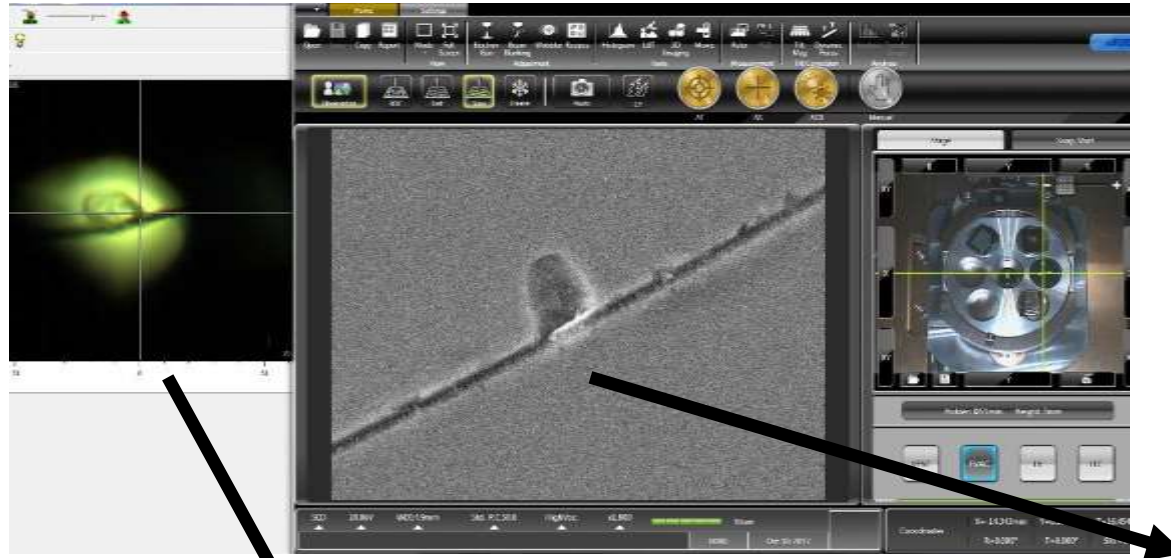
# Crystal Formation in TDS

Failure to control crystal size and distribution could result in:

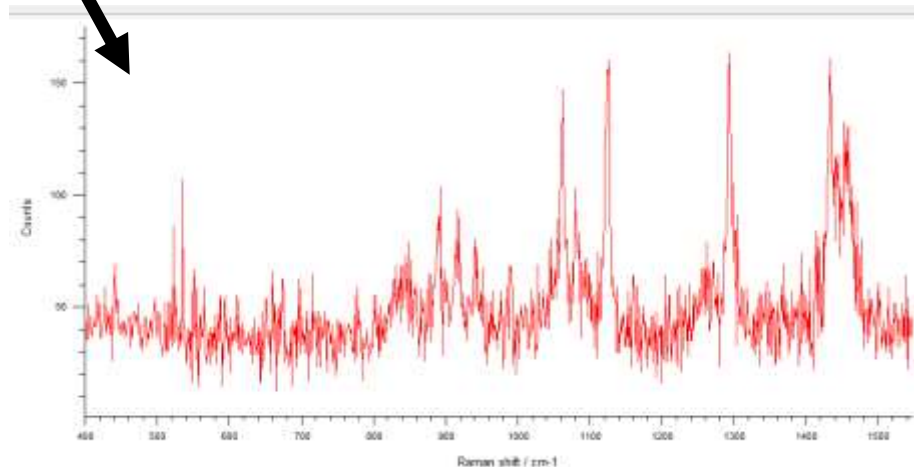
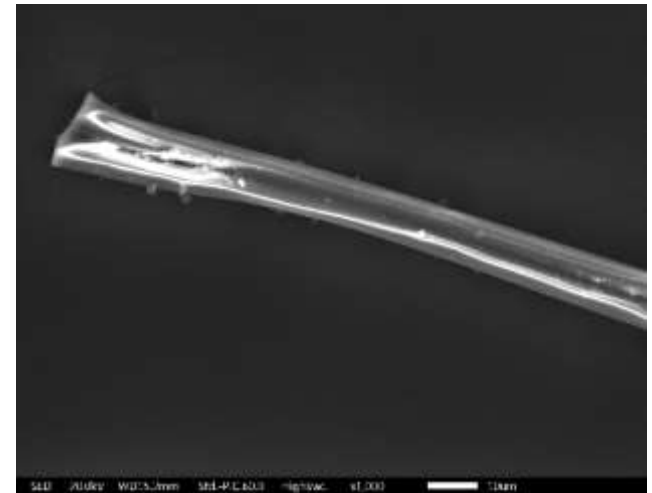
- Skin irritation
- Loss of adhesion
- Reduction in drug delivery
- Uneven appearance



# Chemical and Physical Profiling Crystals



SEM/Raman





# Proton Pump Inhibitors (PPIs)

- Widely prescribed class of drugs in the US
- Used to manage acid-related disorders<sup>1,2</sup>

**Esomeprazole Magnesium  
Delayed Release Capsules**

**RLD: Nexium®**



- Granules may be delivered using oral syringe and nasogastric tube in patients with difficulty swallowing
- Formulated with an enteric coating to prevent degradation in stomach acid

1. Richardson, P.; Hawkey, C. J.; Stack, W. A. *Drugs* **1998**, *56*, 307-335.

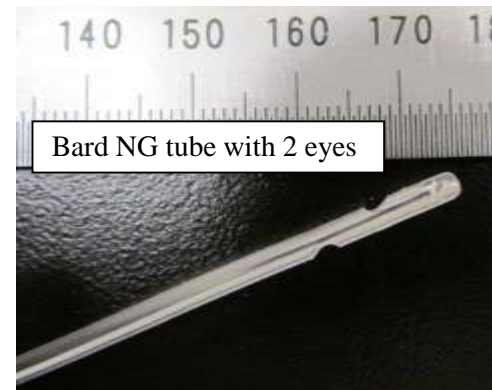
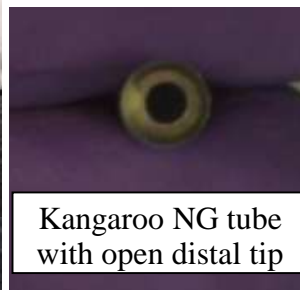
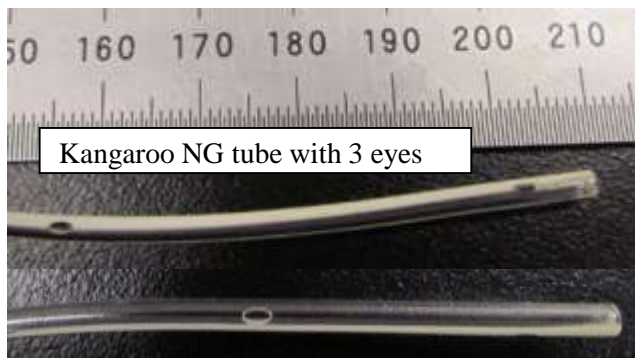
2. Johnson, D. A.; *Expert Opin. Pharmacother* **2003**, *4*, 253-264.

# Drug Delivery through Enteral Feeding Tubes

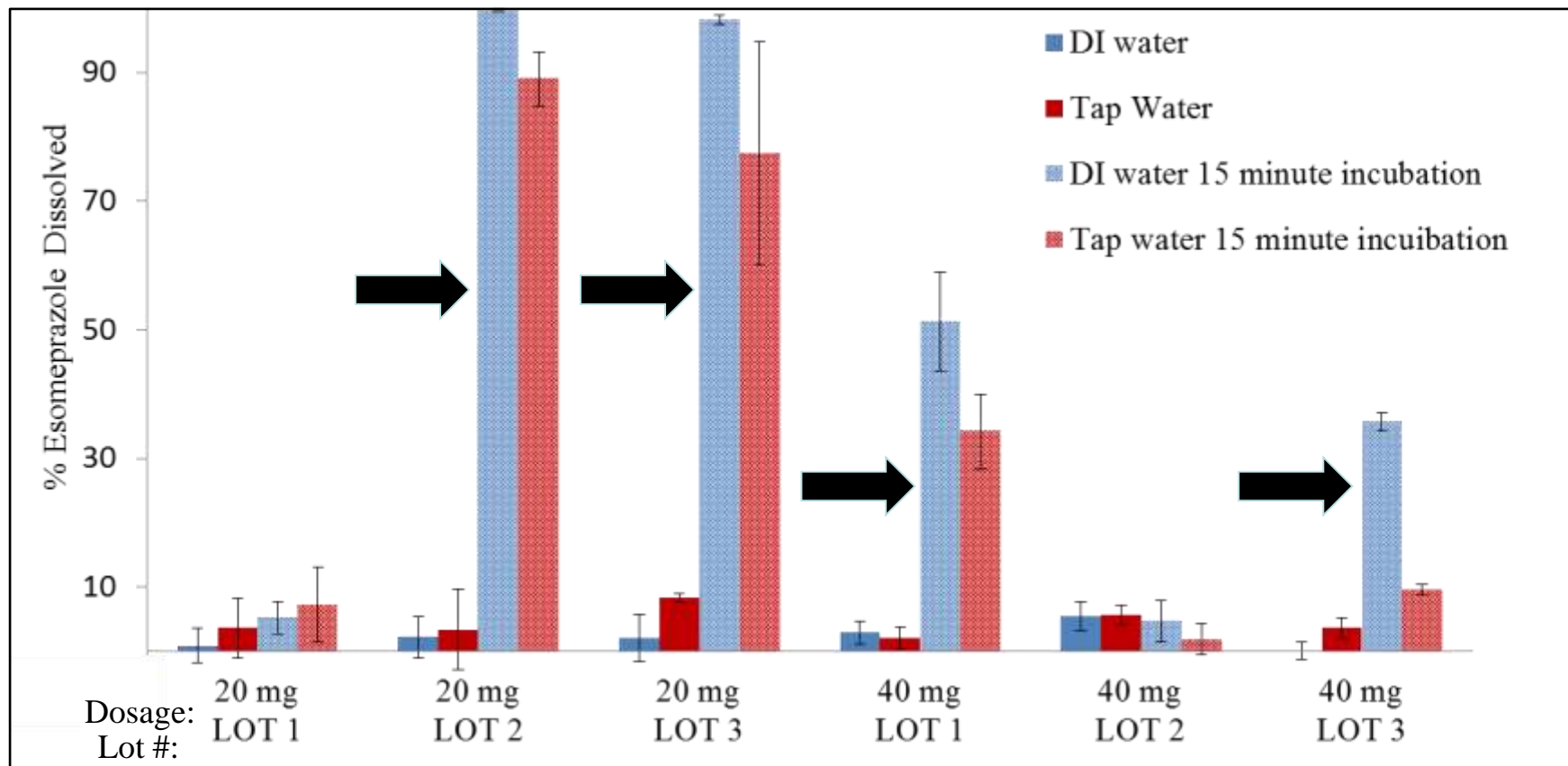


## Considerations/Risk Factors:

- Size, composition, and geometry of tube
- Oral syringe (size, lubricant)
- Water source and pH used to disperse and deliver drug



# Acid Resistance Stability



- All lots passed the acid resistance test when delivered immediately
- Four out of six lots had >10% released when delivered after a 15 min incubation time

# Inhalation Studies: Nasal Sprays

- Particle size of active ingredient impacts quality
  - Effectiveness
  - Bioequivalence (for evaluating generic drugs)
- Challenges in measuring particle size
  - Active and inactive ingredient particles co-exist
  - Polymorphic forms of active ingredient may be present

# Morphology Directed Raman Spectroscopy (MDRS)



- Automated imaging & Raman spectroscopy combined



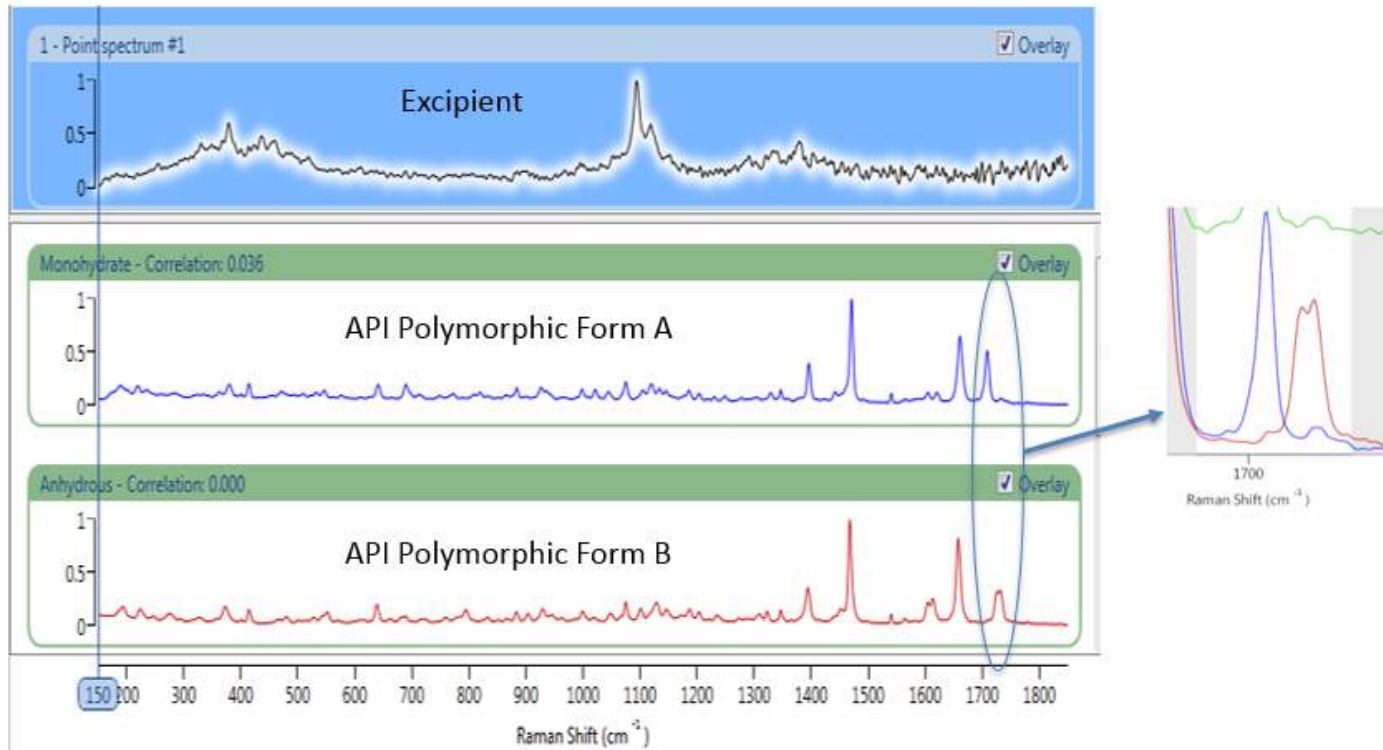
## Morphology Screening

- Classification based on particle morphology

## Raman Confirmation

- Chemical identity of individual particles

# Raman for Chemical ID



- Chemical identification for each individual particle
- Identify different polymorphic forms of an API

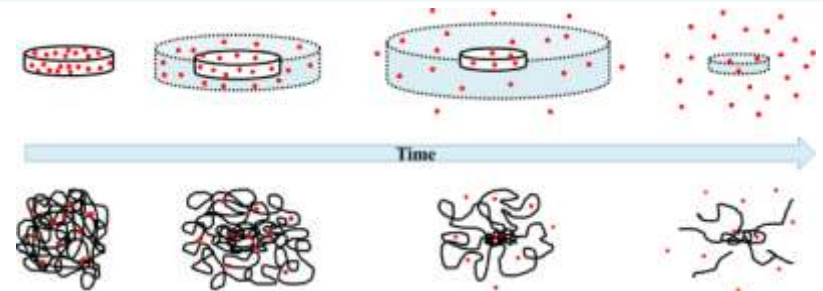
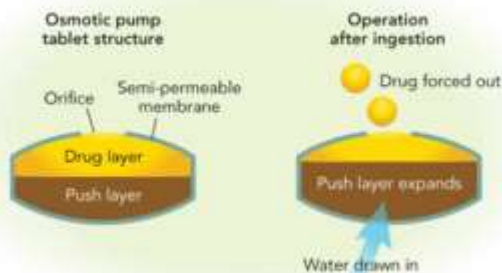


# Nifedipine ER Tablet Dissolution

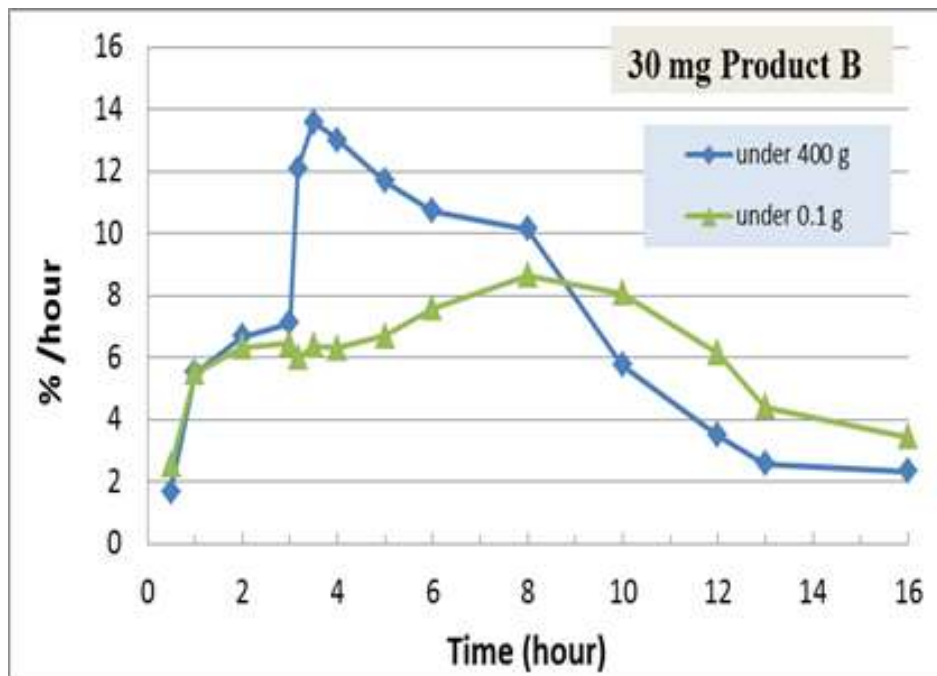
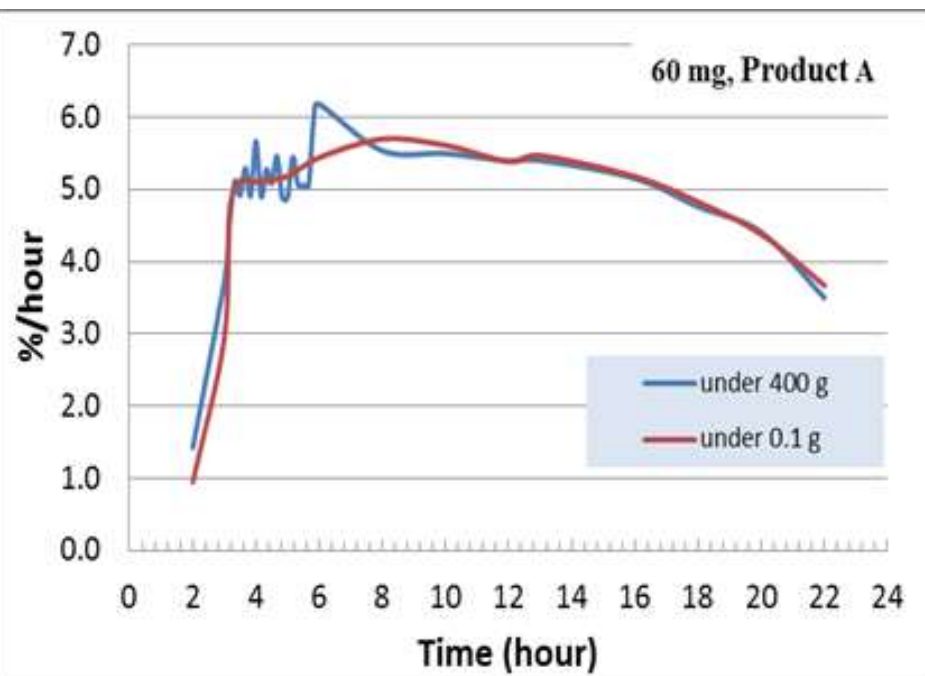


**Brand-Name: Osmotic pump system  
(Product A)**

**Generic: Polymer matrix formulation  
(Product B)**



# Effect of Compression on Nifedipine ER Tablets



Under 400 g compression, the matrix-based formulation showed a greater than two-fold increase in dissolution rate (i.e., G.I. contraction dose dumping)



# Summary and Conclusions

- Generic drug science and research are an integral part of OTR's work
- Science provides a foundation for research readiness
- Research facilitates streamlined evaluation and monitoring of generic drug quality and equivalence to brand-name drugs
- Science and research together promote the development of proactive tools

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Questions:

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