Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products

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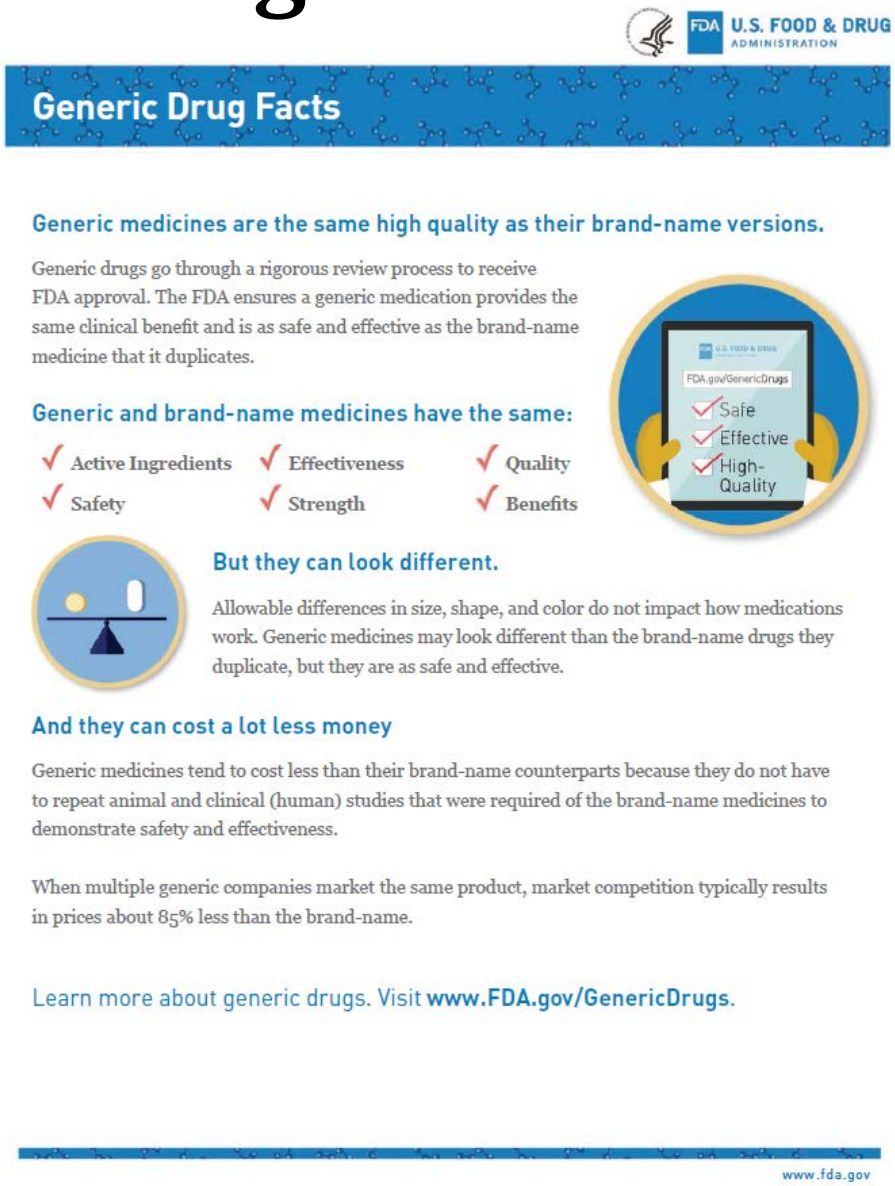
Generic Drugs

- In U.S., 9 out of 10 prescriptions filled are for generic drugs.
- Generic drugs are subjected to a review process prior to approval.
- Generic drugs must be similar to brand name drugs in key attributes:
  - Active ingredient
  - Safety
  - Effectiveness
  - Strength
  - Quality



U.S. FOOD & DRUG ADMINISTRATION

Generic Drug Facts

Generic medicines are the same high quality as their brand-name versions.

Generic drugs go through a rigorous review process to receive FDA approval. The FDA ensures a generic medication provides the same clinical benefit and is as safe and effective as the brand-name medicine that it duplicates.

Generic and brand-name medicines have the same:

- Active Ingredients
- Effectiveness
- Quality
- Safety
- Strength
- Benefits

But they can look different.

Allowable differences in size, shape, and color do not impact how medications work. Generic medicines may look different than the brand-name drugs they duplicate, but they are as safe and effective.

And they can cost a lot less money

Generic medicines tend to cost less than their brand-name counterparts because they do not have to repeat animal and clinical (human) studies that were required of the brand-name medicines to demonstrate safety and effectiveness.

When multiple generic companies market the same product, market competition typically results in prices about 85% less than the brand-name.

Learn more about generic drugs. Visit **www.FDA.gov/GenericDrugs**.

www.fda.gov

OTR's Proactive Science Approach

- OTR has a robust **science** and **research** portfolio.
- The **science program** is designed to maintain a state of preparedness to be able to perform testing and investigations.
  - Consumer complaints
  - Rapid response for public health issues
- The **research program** is "forward looking" in developing tools to evaluate quality and performance of drugs.
  - Emerging technologies
  - Advanced analytics (instrument and modelling)
  - Complex Drugs

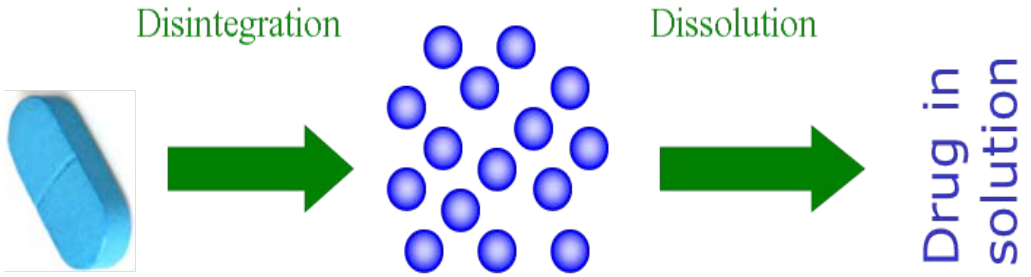
What are Complex Drug Products?

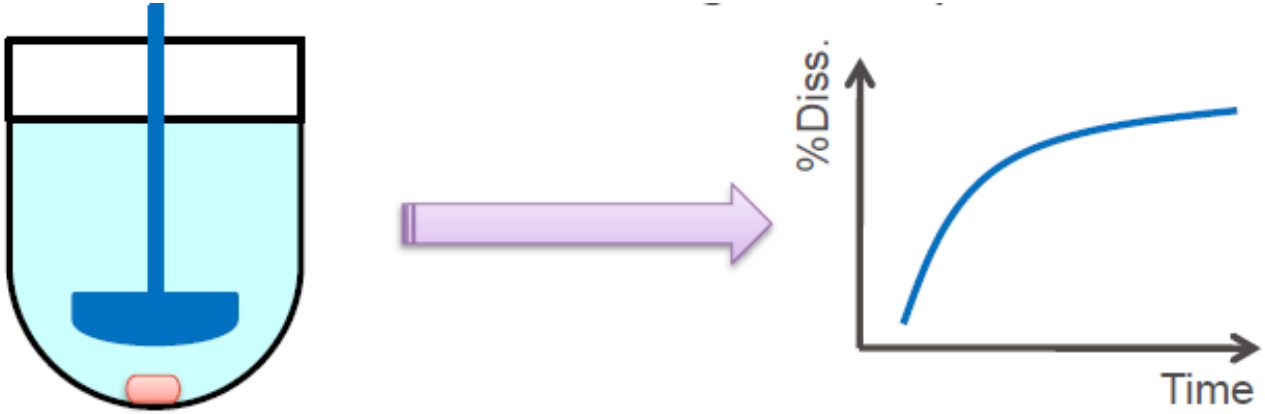
- Complex Active Ingredients
  - Low molecular weight heparin (LMWH), peptides, complex mixtures, natural source products
- Complex Formulations
  - Liposome, iron colloids
- Complex Route of Delivery
  - Locally acting drugs
- Complex Drug-Device Combinations
  - Dry powder inhaler (DPI), metered-dose inhaler (MDI), nasal spray, transdermal system

OTR's Role in Generic Drug Science

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

Dissolution Testing





USP Dissolution Toolbox

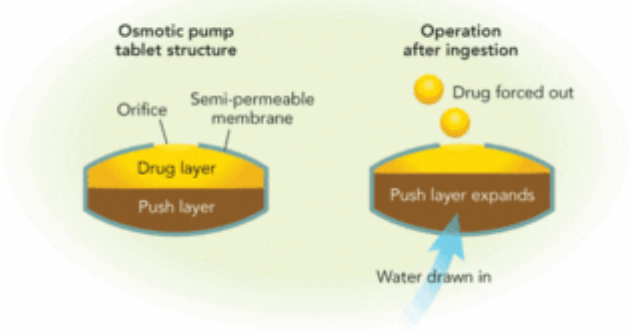
- **Apparatus 1 - Basket** (37º)
- **Apparatus 2 - Paddle** (37º)
- **Apparatus 3 - Reciprocating Cylinder** (37º)
- **Apparatus 4 - Flow-Through Cell** (37º)
- **Apparatus 5 - Paddle over Disk** (32º), Transdermal Delivery System, use paddle and vessel from Apparatus 2 with a stainless steel disk assembly to hold the transdermal on the bottom of vessel.
- **Apparatus 6 - Cylinder** (32º), Transdermal Delivery System, use Apparatus 1 except replace the basket shaft with a stainless steel cylinder element.
- **Apparatus 7 - Reciprocating Holder**, for transdermal delivery systems and also a variety of dosage forms

Beyond the USP Toolbox

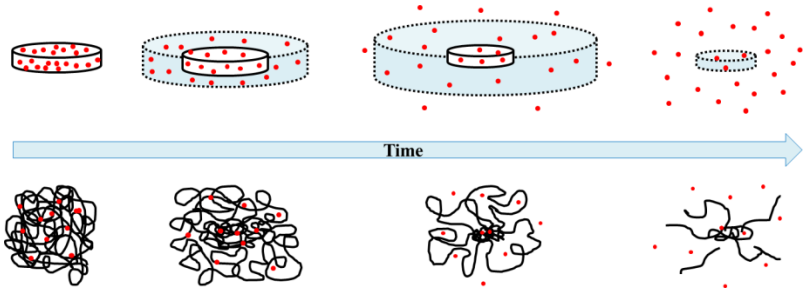
- Non-compendial dissolution models need to be developed because not all drugs have USP methods.
- Use of new technologies for product development and comparison of generic and brand-named drugs.
  - Artificial stomach duodenal model (ASD)
  - FloVitro (DOW)
  - Gastro-Intestinal Model (TIM/TNO)
  - Dynamic gastric model (DGM/IFR)
  - Combined dissolution-absorption models
  - Dissolution models which simulate GI physical stress forces
  - Computational tools/models

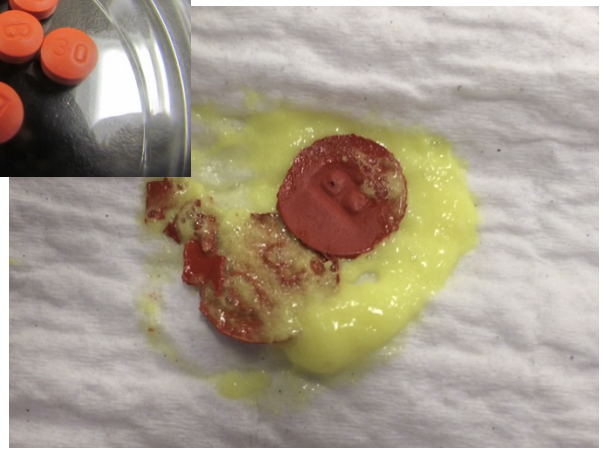
Nifedipine ER Tablet Dissolution

Brand-Name: Osmotic pump system (Product A)

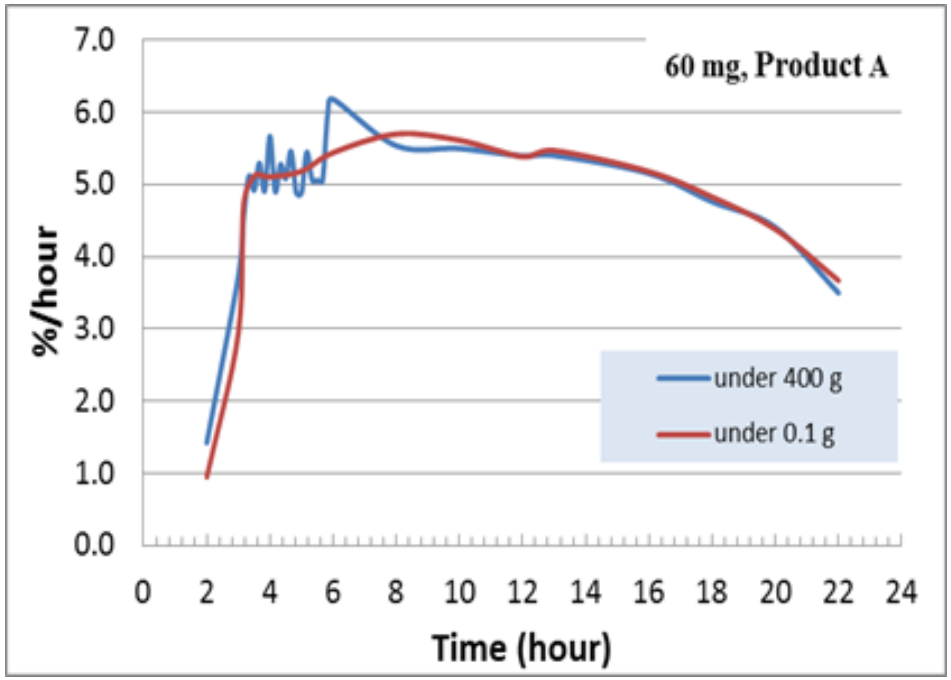


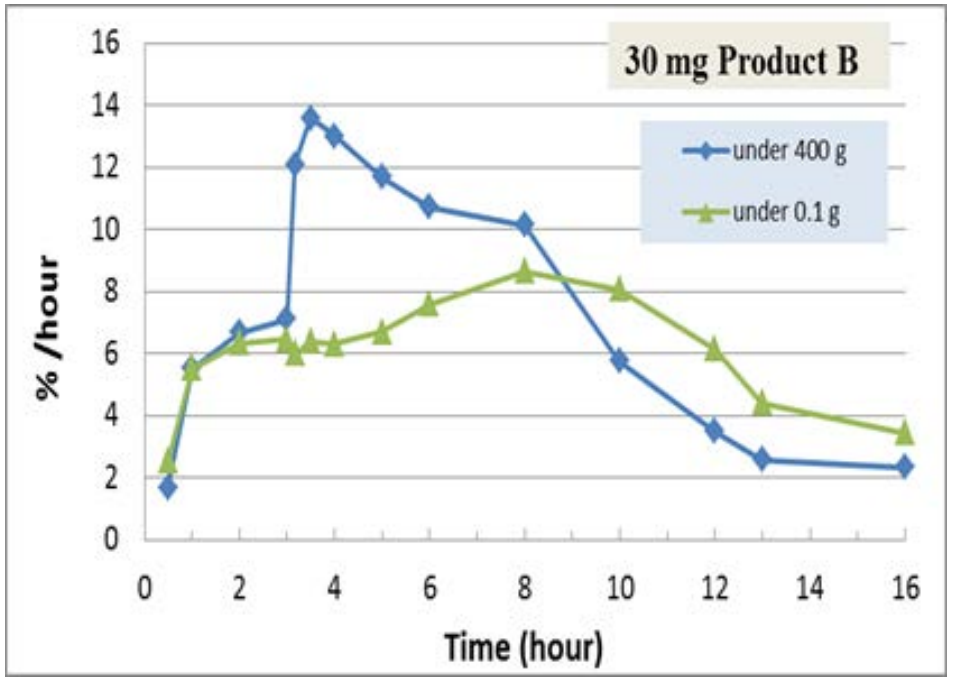
Generic: Polymer matrix formulation (Product B)





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).

Nifedipine ER Tablets Under Compression

- Compared to the osmotic pump formulation, the mechanical properties of polymer matrix-based formulation changed significantly under simulated gastric contraction.
- Contraction-induced dose-dumping from the matrix-based polymer formulation was observed.
- A dissolution apparatus which can apply compression forces can aid formulation scientists performing product development and provide the regulatory agency with additional measurements to assure the quality of drug products.

Inhalation Studies

- Particle size of active pharmaceutical ingredient (API) is a critical attribute in evaluating nasal spray suspension products.
  - Quality
  - Effectiveness
  - Bioequivalence (for evaluating generic drugs)
- Challenges
  - Active ingredient and excipient particles co-exist in formulation
  - Drugs containing combination of active ingredients
  - Polymorphic forms of active ingredient

Morphology Directed Raman Spectroscopy (MDRS)

- MDRS, as an emerging technology, shows potential to answer inhalation product questions.

<u>Automated imaging & Raman spectroscopy combined in one integrated platform</u>

Morphology Screening

- Classification based on particle morphology: separate particles based on their similarities in size, shape, and other physical features.

Raman Confirmation

- Chemical identity of individual particles based on spectral matching to library spectra of API

Attributes Monitored by MDRS

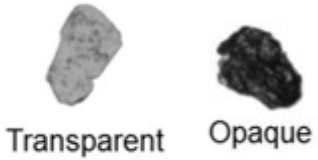
Shape:

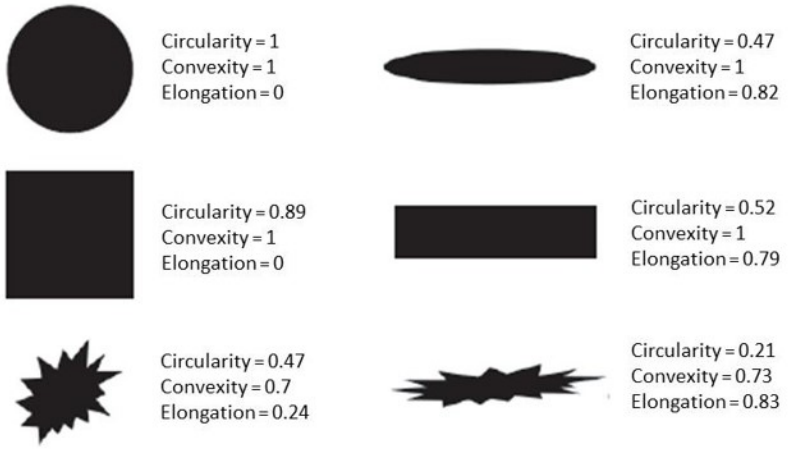
- Aspect Ratio: width / length
- Elongation: defined as [1-aspect ratio] or [1-width/length]
- Circularity: ratio of the perimeter of circle with the same area as the particle divided by the perimeter of the actual particle image
- Convexity: perimeter of a particle divided by its convex hull perimeter
- Solidity: area of a particle divided by its convex hull area.

Other physical features:

- Intensity Mean
- Intensity SD

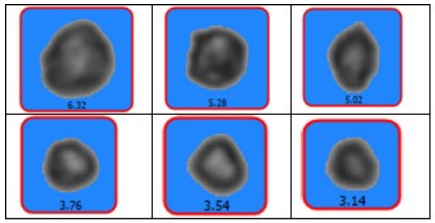
Measurements of light transmission or light reflection of the particles.



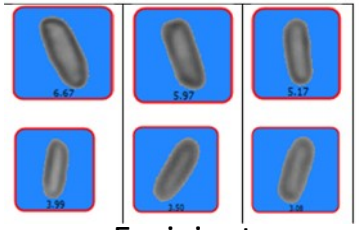


Why Morphology Measurements?

API and excipient particles may have different morphologies.



API



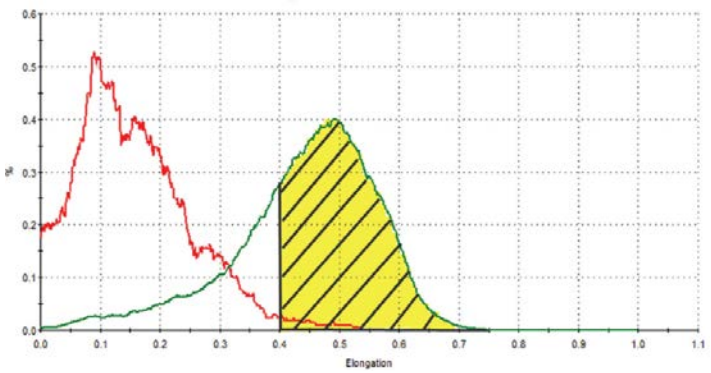
Excipient

Advantages:

- ✓ Fast measurement.
- ✓ Fast data processing.

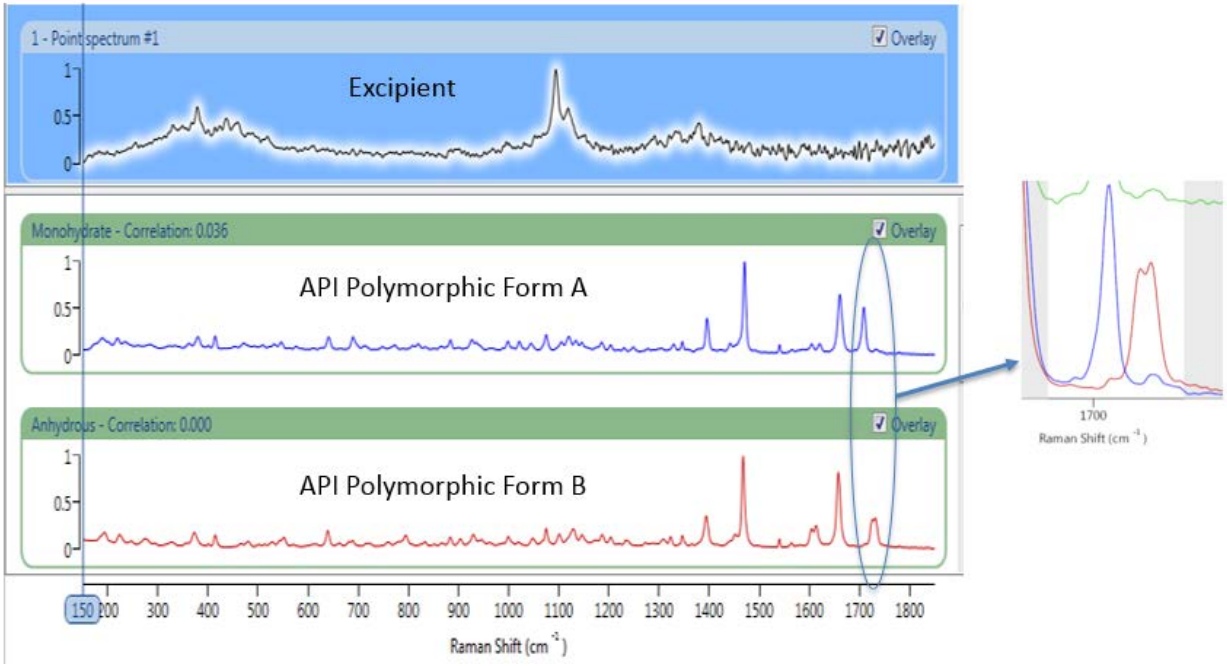
Disadvantage:

- ❖ Cannot completely separate API and excipient particles due to particles with overlapping morphological feature.



<u>Morphology measurement is a great screening tool, but not good enough to provide conclusive results.</u>

Raman for Chemical ID



Raman Advantages:

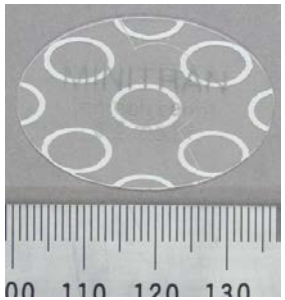
- ✓ Chemical identification for each individual particle.
- ✓ Identify different polymorphic forms of an API.

Raman Disadvantage:

- ❖ **Slow measurement, time-consuming.**

Transdermal Delivery Systems

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



TDS-Release Liner Studies

Consumer complaints:

- Patch won't separate from tabs
- Patch won't peel cleanly away from liner
- Medication is sticking to the plastic tabs

- Release liner test:
  - Measures the force required to peel away the TDS from its release liner

- Objectives:
  - To establish sample preparation and instrument parameters for measuring liner adhesion of TDS and to determine the range of release liner adhesion values for various TDS.

TDS-Cold Flow Studies

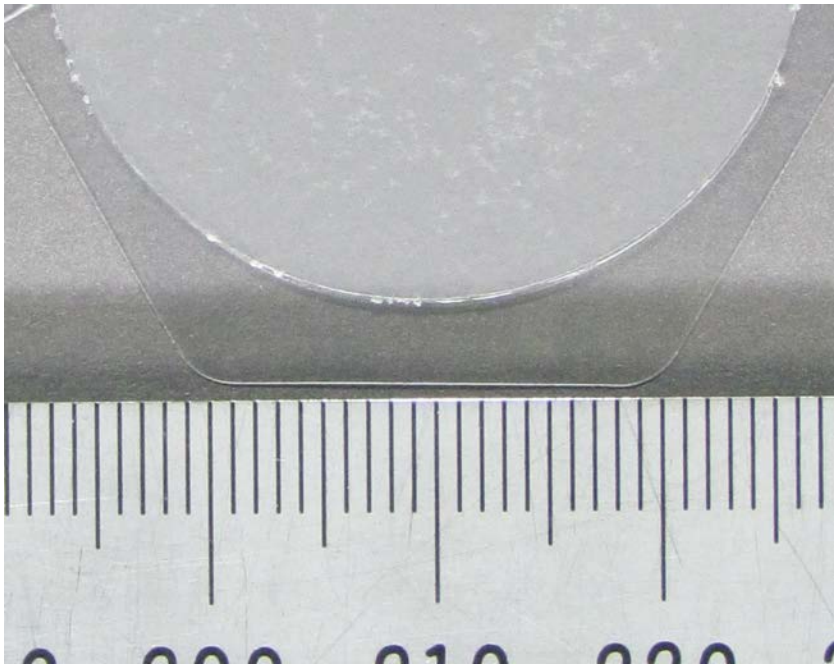
- "Cold flow," "adhesive ooze," "bleed"
- Adhesive residue on the TDS outer edges, release liner, or pouch
- Can be present on matrix systems and reservoir systems

Objective: Compare methods to evaluate cold flow.

Crystal Formation in TDS

Failure to control crystal size and distribution could result in:

- skin irritation
- loss of adhesion
- reduction in drug delivery
- an appearance that suggests the manufacturing process is not under control



Objective: Use scanning electron microscopy (SEM) and Raman spectroscopy to identify crystallization in TDS.

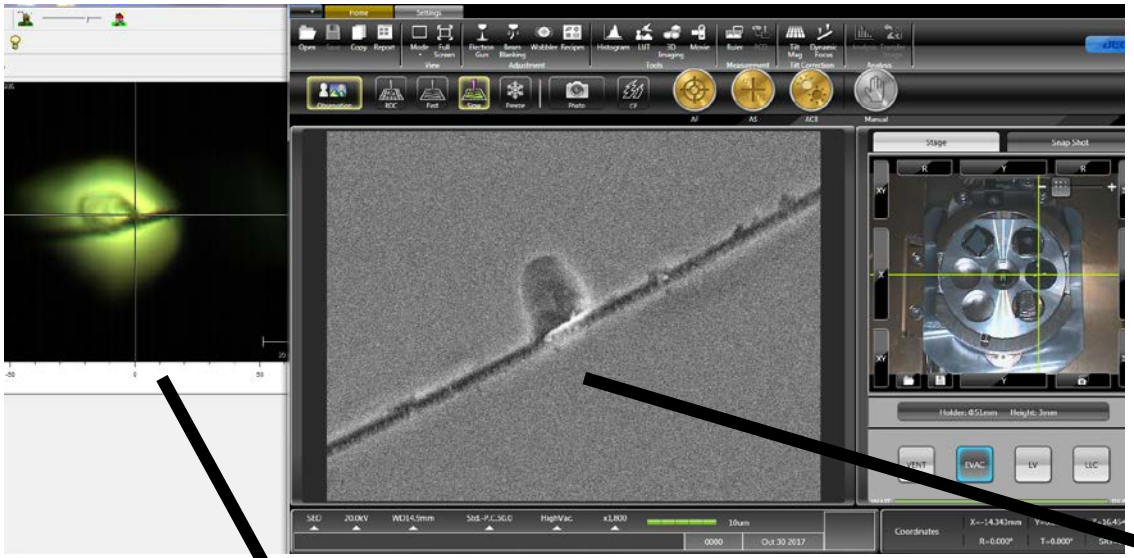
SEM-Raman System

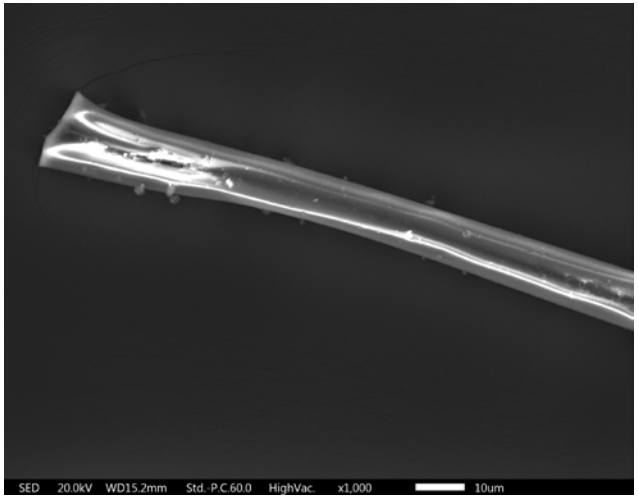
- SEM: JEOL IT300LV
  with low vacuum, rotating stage, air lock chamber and system, Energy Dispersive X-ray, cryotransfer system

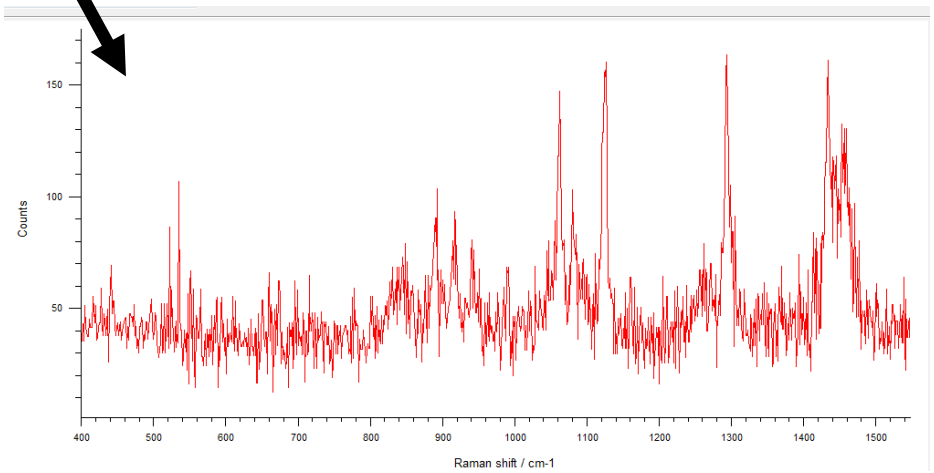
- SEM-SCA (Structural and Chemical Analyzer) Interface permits **simultaneous** secondary electron imaging and Raman spectroscopy inside SEM making chemical analysis possible within the SEM

- Raman: Renishaw inVia Reflex spectrometer and microscope
  785 nm laser, 5X, 20X, 50X, 100X

Chemical and Physical Profiling







Summary and Conclusions

- Generic drug science and research is an integral part of OTR's work.
- Generic drug science provides a foundation for research readiness' that anticipates future needs and allows for rapid response.
- Generic drug research facilitates streamlined evaluation and monitoring generic drug quality and equivalence to brand-name drugs.
- Generic drug science and research promotes the development of proactive tools that can be used to monitor drugs throughout the lifecycle of both generic and brand-name products.

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Questions:

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