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NIPTE The National Institute for Pharmaceutical Technology and Education

Improving quality and lowering costs of pharmaceuticals

Foundations of in vitro comparisons of generic opioids to reference listed drugs (RDLs) with labeling describing abuse-deterrent properties

Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products
Sheraton, Silver Spring, MD

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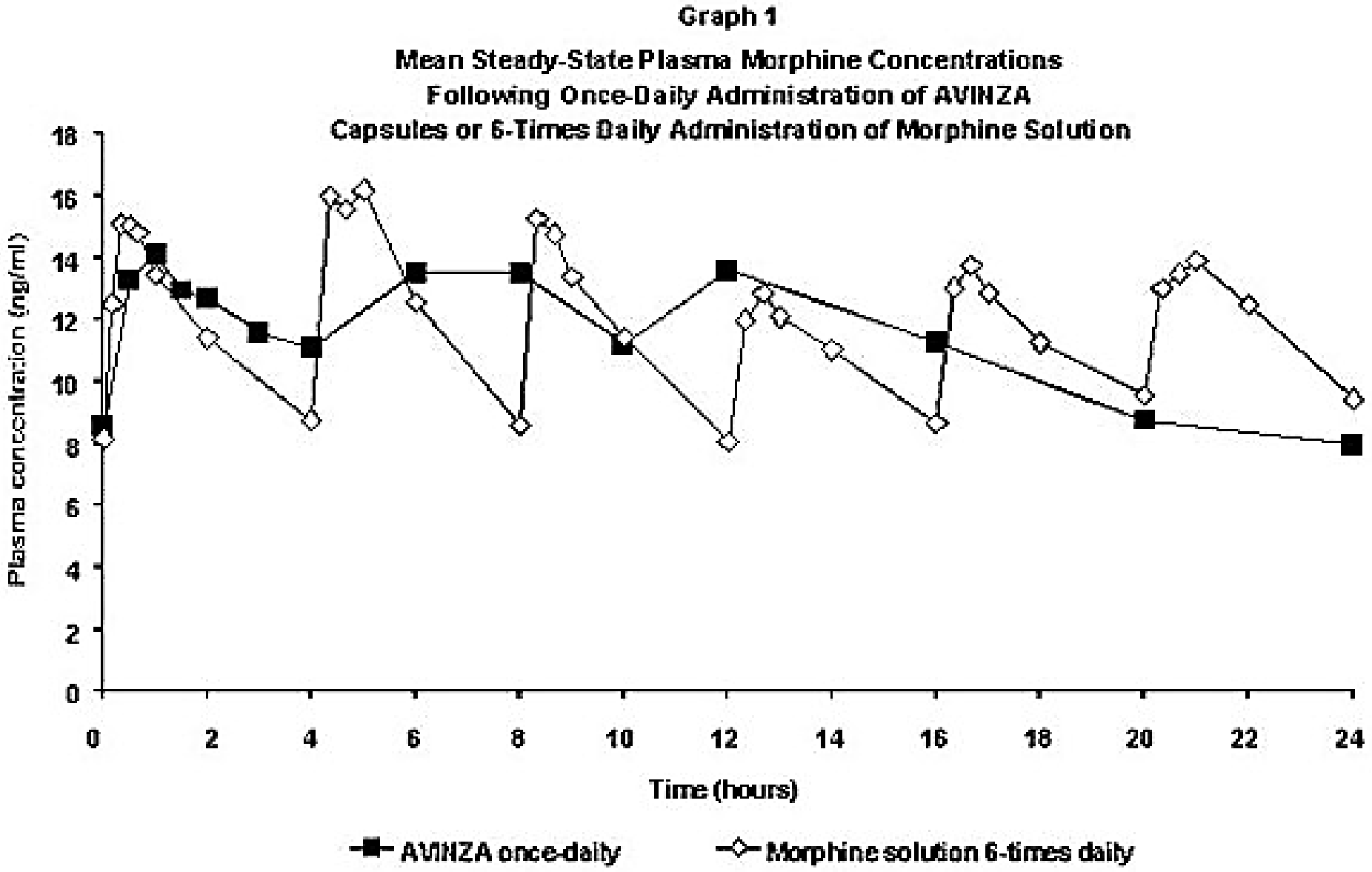
Outline

- Introduction
- Material Science principles applied to Abuse Deterrent Formulation testing
- Testing of manipulated products
- Summary

Once-a-day Dosing of Opioids



Goals

- **Goal of abuser**
  - **Manipulate product such that:**
    - **Absorb as much drug as possible in the shortest period of time possible**
  - **Rapid release or dose dumping creates**
    - **↑ C_{max}**
    - **↓ t_{max}**
    - **Such that**
      - **→ Pharmacokinetic change**
      - **→ Pharmacodynamic response change**
      - **→ Creates euphoria or abuser's "reward"**

- **Goal of Abuse Deterrent Formulation (ADF)**
  - **Create barriers to prevent dose dumping**
    - **Chemical**
    - **Physical**
  - **Create situation where it is undesirable for abusers to manipulate product**

Modes of Abuse

- **Snort**
  - **Reduce particle size**
  - **Absorption in nasal cavity**
    - **What is not absorbed nasally is absorbed via GI tract**
- **Smoke**
  - **Vaporize after reducing particle size**
  - **Absorption in lungs**
- **iv**
  - **Reduce particle & extract in solvent**
  - **No absorption direct iv injection**
- **Oral**
  - **Reduce particle size or exceed recommended dose**
    - **Absorption in GI tract**

Abuse Deterrent Strategies

Approach	Example
Physical/chemical barriers	
Physical resistance to crushing	Polyethylene oxide matrix oxymorphone ER
Gel based or gel forming	Polymer matrix embedded oxycodone CR
Agonist-antagonist combinations	
Sequestered antagonist with Differential bioavailability	Morphine/naltrexone Buprenorphine/naloxone
Aversive components	
Aversive oxycodone IR	Hydrocodone/acetaminophen
Prodrugs	Lisdexamphetamine
Combination of methods	In development
Novel approaches	Yet to be developed

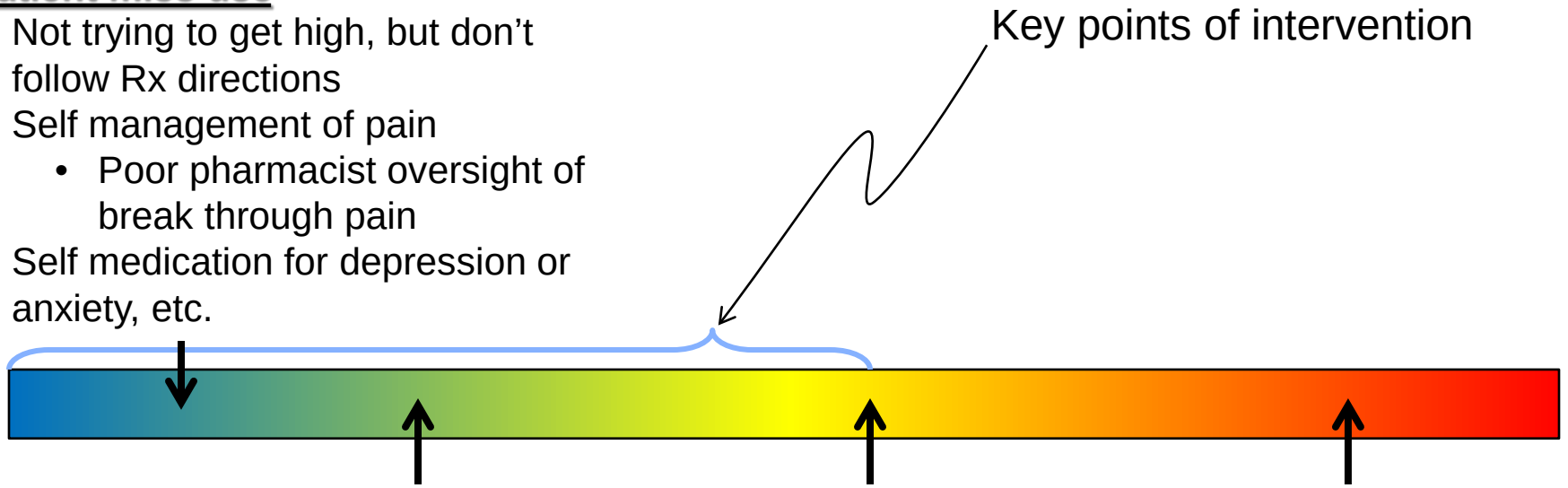
Approved Abuse-Deterrent Opioid Products

NDA	API	Brand	Approval	Dosage Form	Possible controls
206627	Hydrocodone	Hysingla ER	11/20/14	ER Tablet	IR Hydrocodone combination tablet
208090	Oxycodone	Xtampza ER	04/26/16	ER Capsule	IR oxycodone capsule
022272	Oxycodone	OxyContin	04/05/10	ER Tablet	IR oxycodone tablet
206544	Morphine	MorphaBond	10/02/15	ER Tablet	IR morphine tablet; Non ADF ER tablet
207621	Oxycodone/ Naltrexone	Troxyca ER	08/19/16	ER Capsule	IR oxycodone capsule
205777	Oxycodone/ Naloxone	Targiniq ER	07/23/14	ER Tablet	IR oxycodone tablet
022321	Morphine/ Naltrexone	Embeda	08/13/09	ER Capsule	Non-ADF ER capsule

Spectrum of Abuse

Patient miss use

- Not trying to get high, but don't follow Rx directions
- Self management of pain
  - Poor pharmacist oversight of break through pain
- Self medication for depression or anxiety, etc.



Curious users

- See what it is like to get high
- Not a lot of experience in drug abuse

Recreational users

- Trying to get high
- May have experience with drug abuse

Addicts

- Trying to get high
- Can be highly motivated
- Disregard all directions
- Willing to take great risks
- Have lots of time

Can progresses to full fledge addiction

Abuse deterrent formulations are not abuse proof

Raffa, R.B. and J.V. Pergolizzi Jr, *Opioid formulations designed to resist/deter abuse.* Drugs, 2010. **70**(13): p. 1657-1675

Test Development for ADF

- **A good *in vitro* test method should be:**
  - **Accurate, precise, robust, stable, etc.**
  - **Simple**
    - **Intra and inter lab reproducibility**
  - **Representative of abuser's actions**
- **Ideally a test method should:**
  - **Correlate with abuser's actions and product performance in the real world**
    - **In bioequivalence parlance IVIVC or IVIVR**
    - **Real world should include Category 4 studies, which are beyond the scope of this talk but is an area where research is needed**

Testing of ADFs

Mode of abuse

- Mechanical
  - Crushing
  - Grinding/abrasion
  - Cutting/grating
- Thermal
  - Heating
  - Freezing
- Extraction
  - Solvent type
  - pH
  - Temperature
  - Hydrodynamics
- Separation
  - Differential extraction of antagonist and aversive agents

Routes of Administration

- Oral
- Inhalation
- Snorting
- Smoking
- Parenteral
- iv injection

Test Method Selection

- Particle size reduction
- Mechanical strength testing
- Extraction testing
- Viscosity & Syringeability
- Dissolution testing
- In vitro models for
  - Snorting
  - Smoking
- Differential extraction of antagonists or aversive agents

Typical Abuser's Toolbox

Mechanical

- Cutting
  - Razor
  - Knife
  - Grater
  - Pill crusher
  - Diagonal cutters
- Crushing
  - Two spoons
  - Mortar and pestle
  - Hammer
- Grinding
  - Abrasive grinding, Dremel® tool
  - Impact grinding, e.g., milling, coffee grinder, food processor

Thermal

- Oven
- Microwave
- Boiling water

Extraction

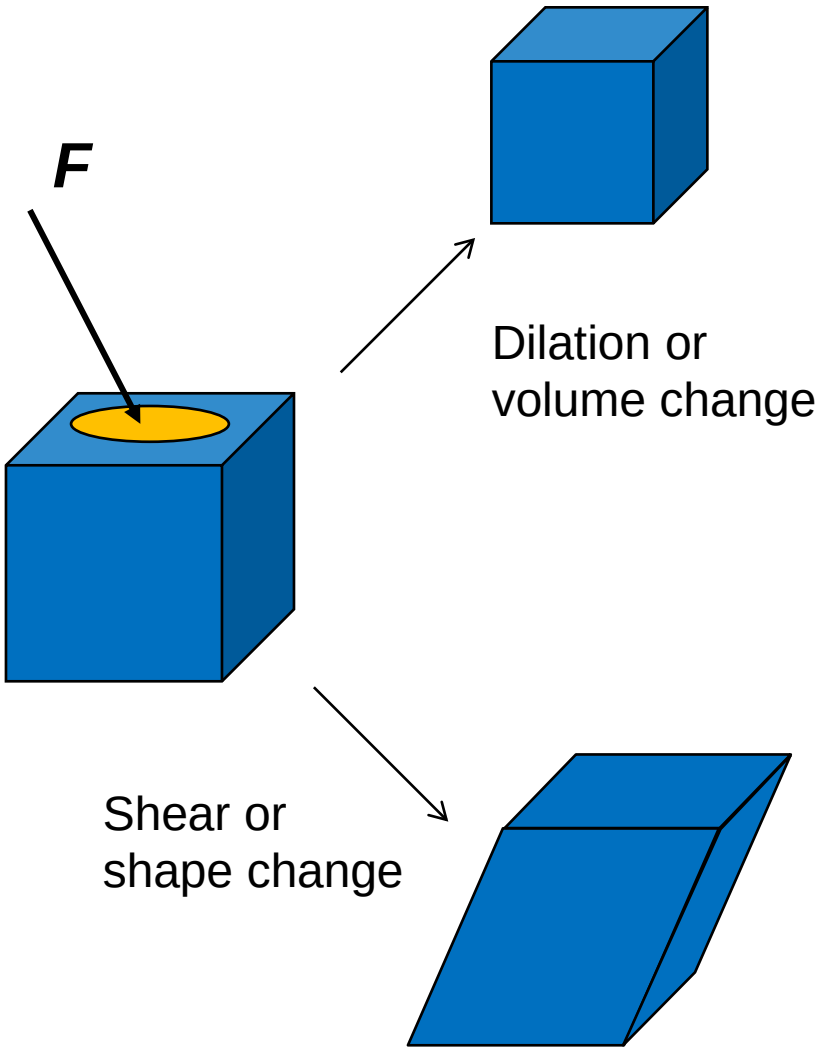
- Solvents
  - Water
  - Finger nail polish remover
  - Rubbing alcohol
- pH
  - Vinegar
  - Baking soda
  - Drano®
- Abuse conditions
  - Agitation rate
  - Extraction time and temp.
  - Etc.

Mimicking House Hold Tools

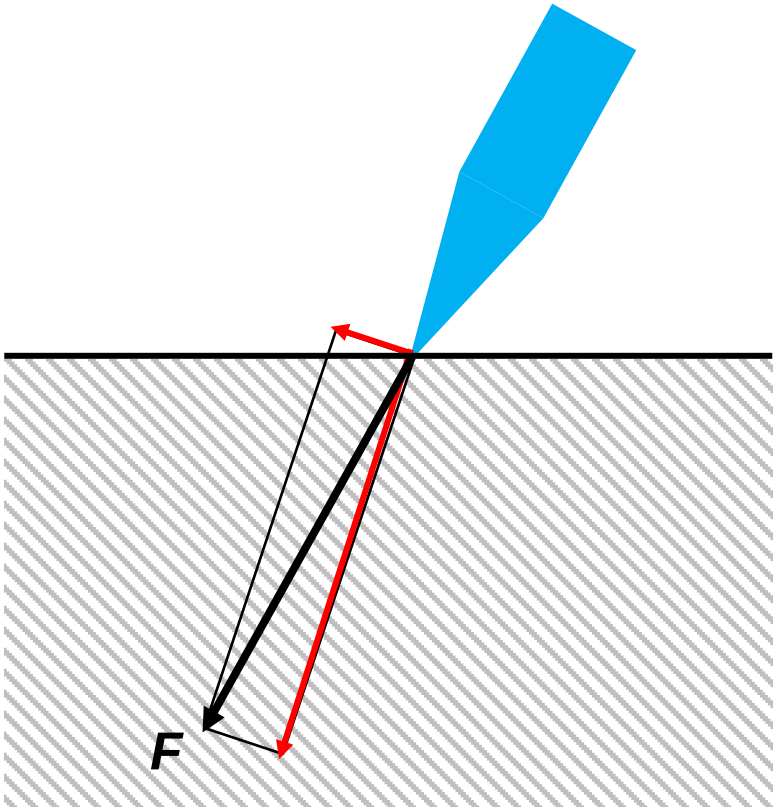
- House hold items are:
  - Highly variable and not designed for reproducible use
  - Often redesigned every few years for marketing reasons
- To test for a given mode of abuse
  - Need to capture principal forces that are used to destroy the barrier
- For testing
  - Need to use forces that are representative of what abusers actually use
  - Need to standardize application of these forces to product
  - Rate of force application is also important

Mechanical Manipulation

- **Application of force to a body causes deformation & eventually fracture**
- **The type of force applied dictates how the body fails**
  - **For example a body can fail in shear or tension**
  - **Bodies have different strengths in shear and tension**
- **The application of any force can be resolved into**
  - **Dilation**
  - **Shear**
- **Much is known about failure and particle size reduction**
  - **Can use this research to develop reproducible test methods**
  - **Assess the forces used by a typical abuser so as to design representative tests for product manipulation**

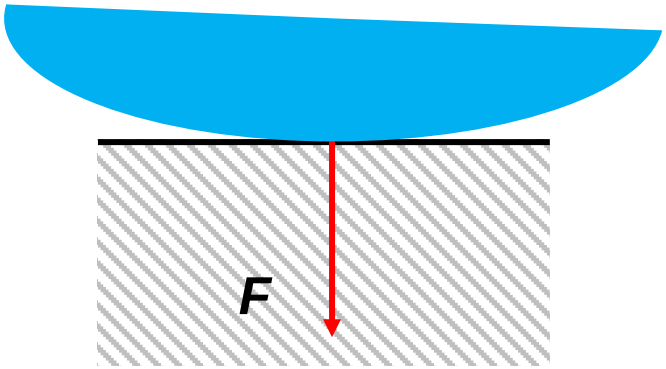


Application of Force: Cutting & Crushing



Cutting with razor blade creates
High Shear Force

Leads to failure in shear

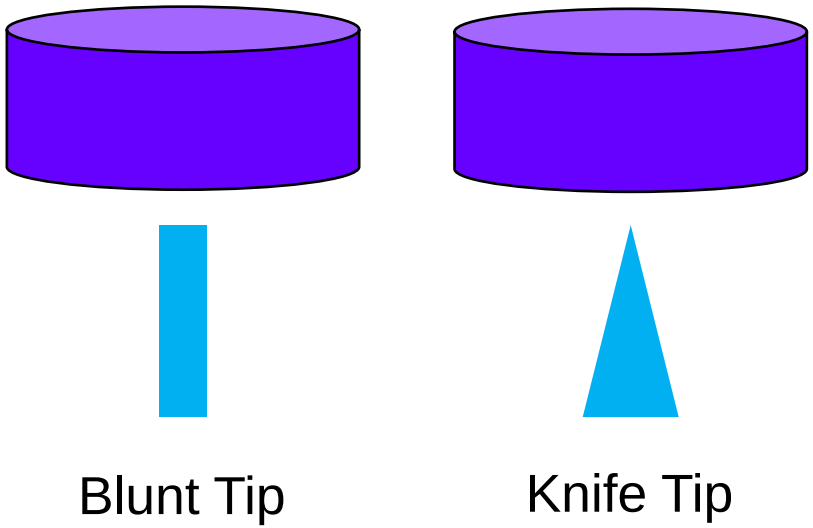


Crushing with spoon creates
High Compressive Forces

Leads to failure in tensile

Milling

- **Key parameter**
  - **Energy / Momentum of impact**
- **Controlled by**
  - **Tip speed**
  - **Tip cross sectional area**



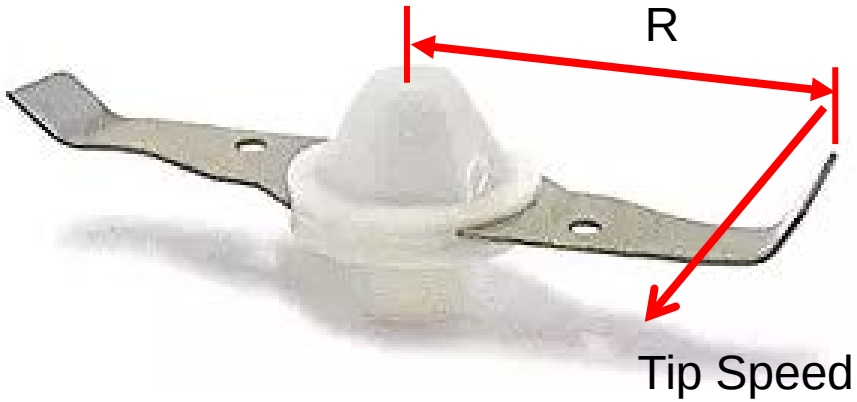
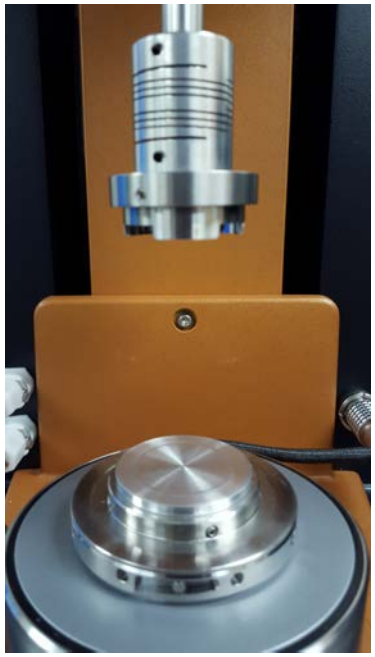


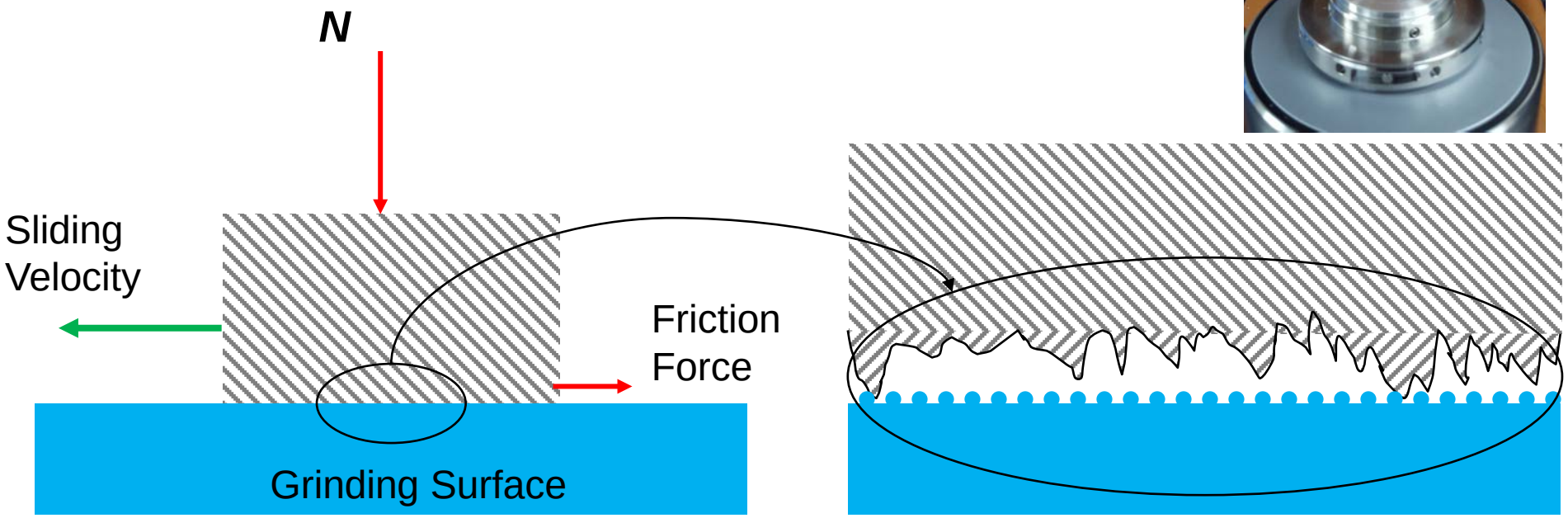
Image Source: Amazon.com

Grinding



Key Parameters

- Normal force (N)
- Sliding velocity
- Surface Texture and Hardness



Grinding with abrasive

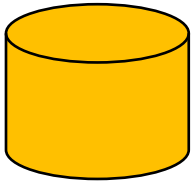
Tribology Interaction between surfaces

Can lead to particle attrition by abrasion

Failure Modes

- **Each abuse deterrent technology has its own failure modes**
  - **E.g.: physical barriers**
    - **Key failure mode**
      - **Destruction of the barrier**
      - **Extraction of the drug**
- **Key scientific questions**
  - **What are the critical quality attributes that affect ruggedness of the barrier**
  - **What are the critical quality attributes of the abused product that affect administration and API uptake**

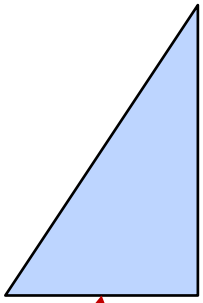
Nasal Route of Abuse



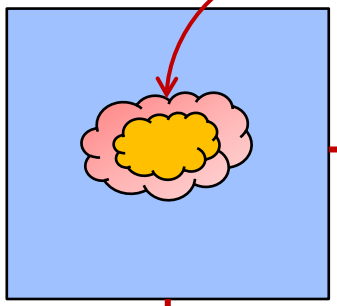
Barrier Destruction

Cutting - Diagonal cutters
Milling - Coffee grinder
Grinding – Dremel® tool

Abuser Factors



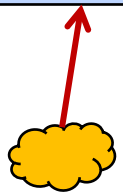
Particles
< 100 μm



ADF gelling layer

Nasal
Absorption

PK Absorption Factors



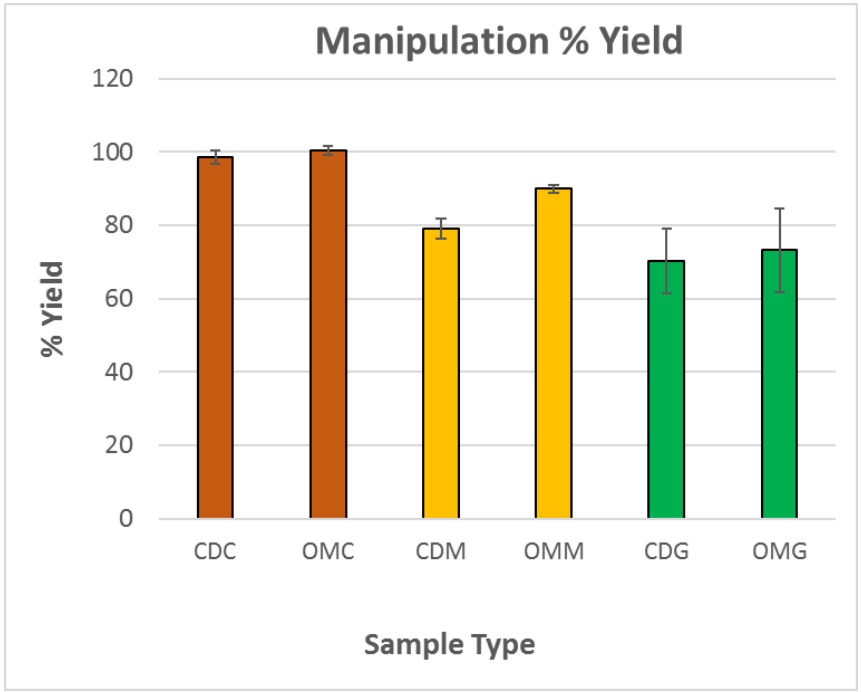
Snorting
Into Nose

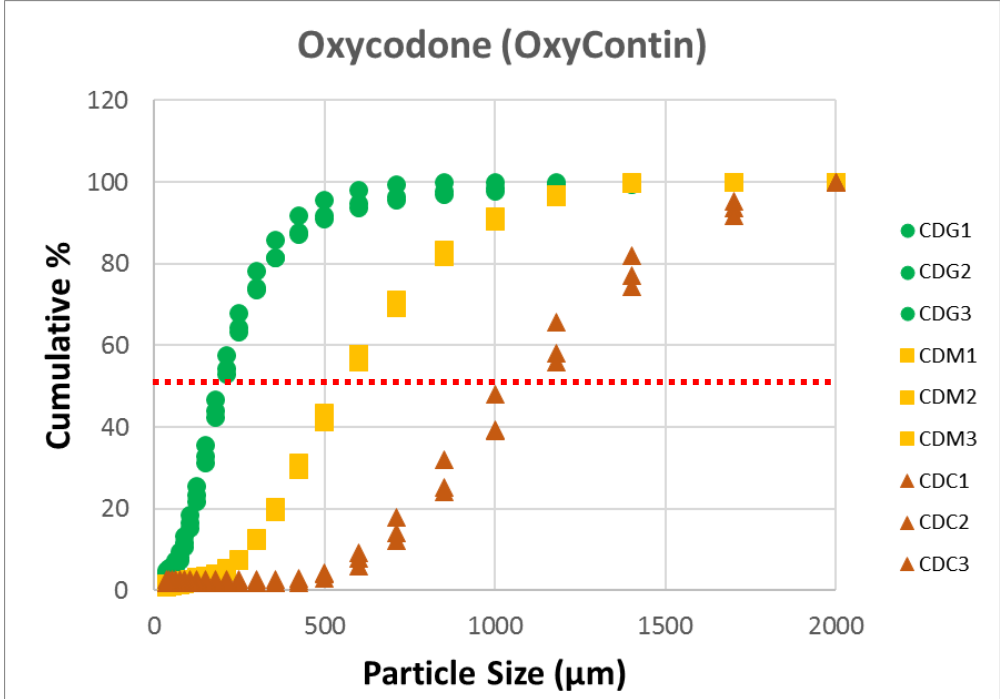
Mucociliary
Clearance to
Nasal Pharynx

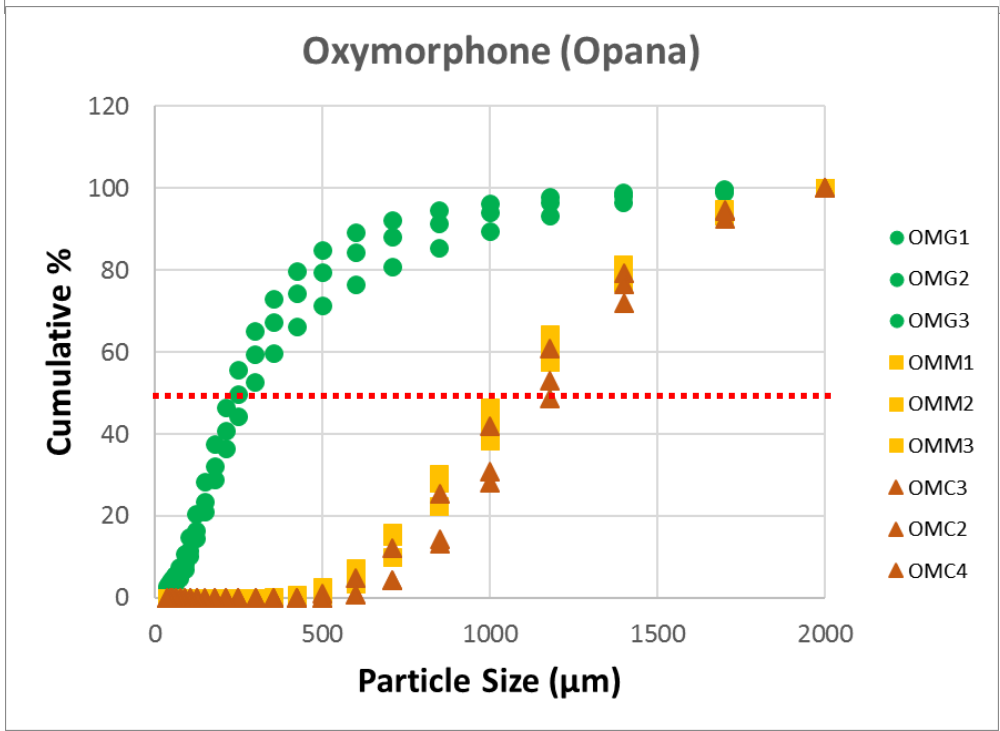
Product Manipulation

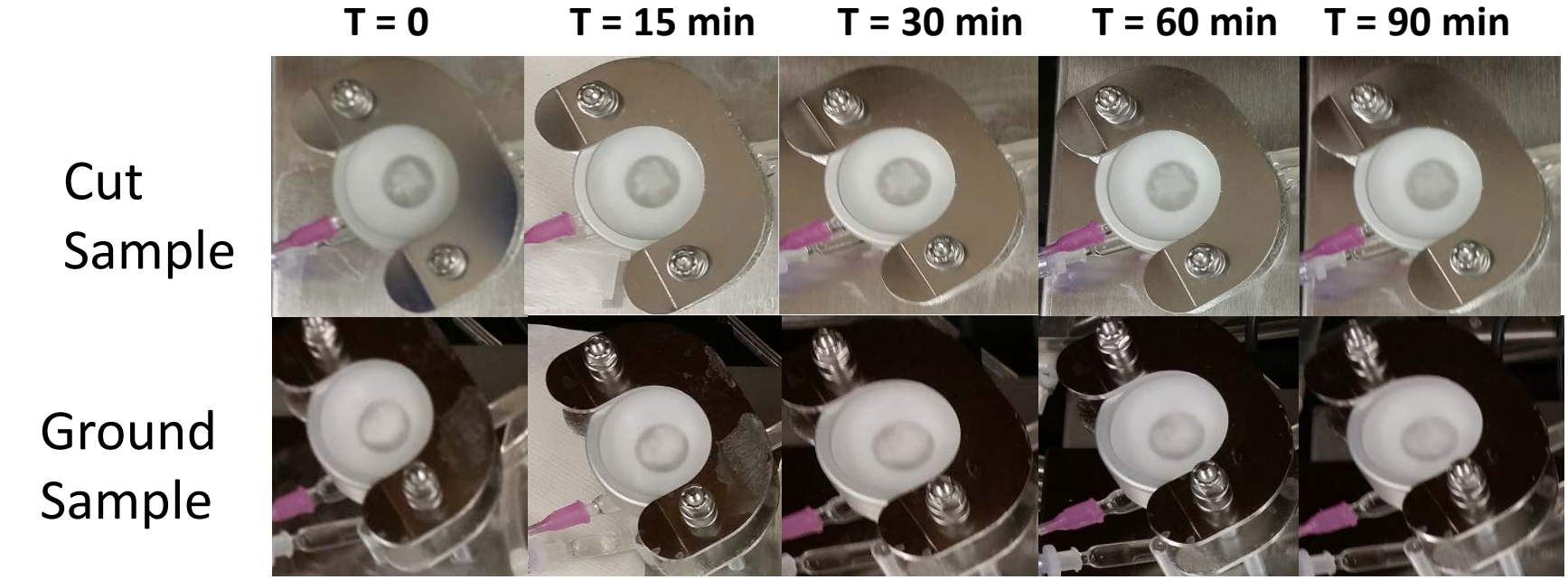
Manipulation Technique

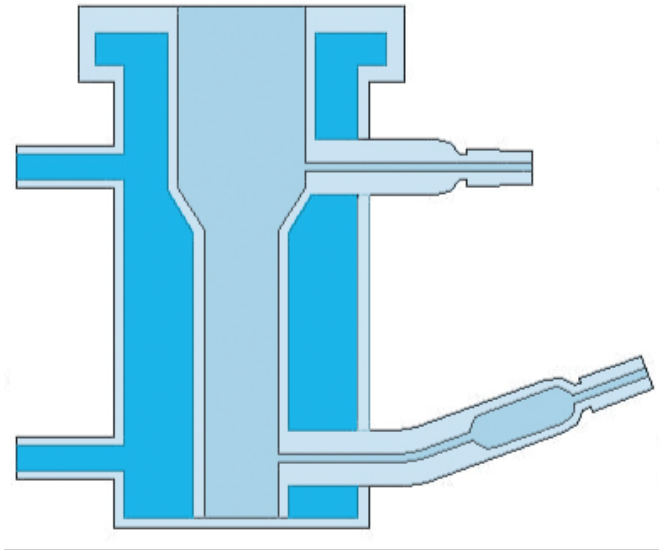
- Has big effect on particle size
- The more energy the finer the particle size
- Plastic materials are hard to mill
  - Require more energy to mill
  - i.e., have a higher milling limit
- Yield is an important factor
  - Plastic materials tend to have lower yield





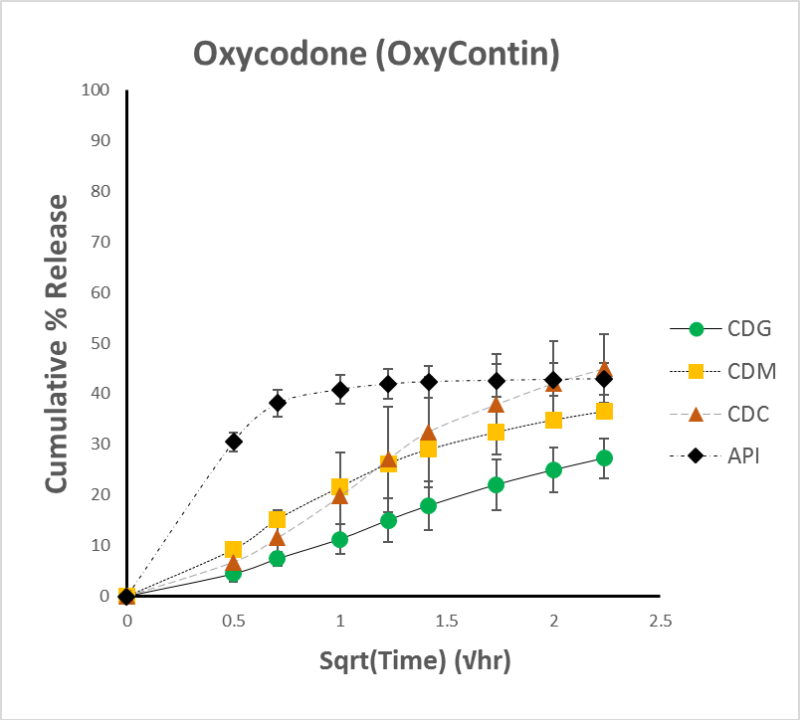


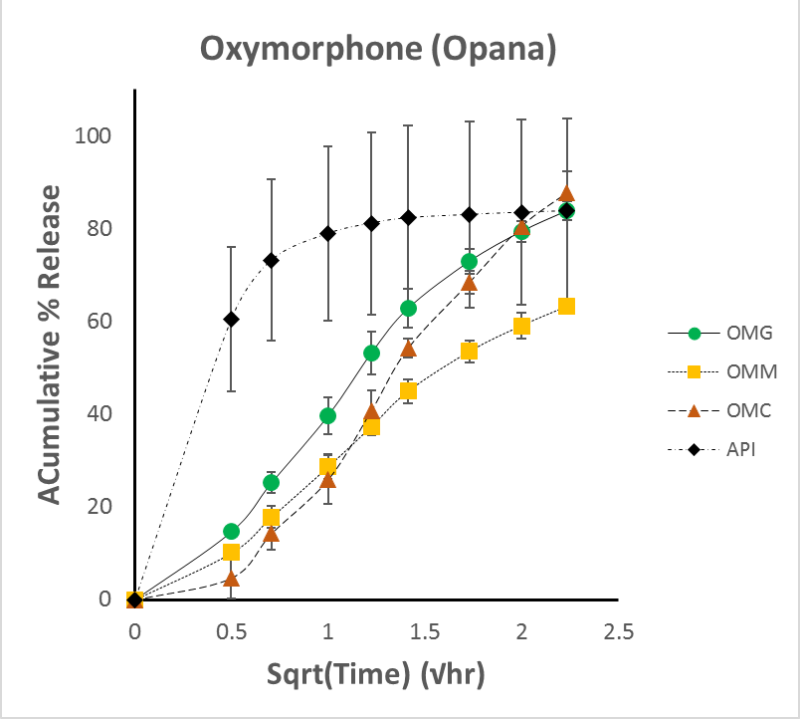

T = 0
T = 15 min
T = 30 min
T = 60 min
T = 90 min
Cut Sample
Ground Sample



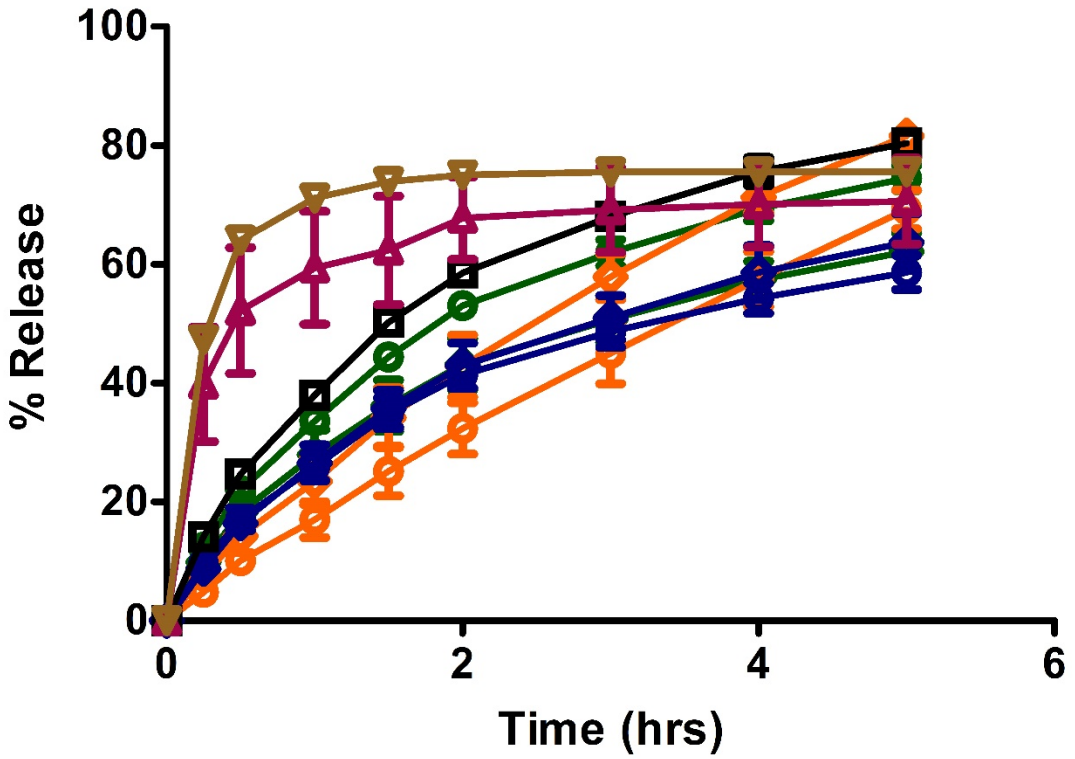
Release Studies

- Vertical diffusions cell
  - Sampled placed on moist membrane
  - Formulation influences release rate, pure API faster than abused product
- Differences in particle size may not always influence release rate
- The correlation/relationship to *in vivo* performance needs to be better understood



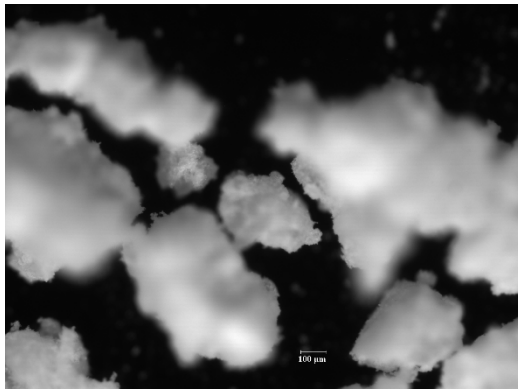


Cumulative % Release Metoprolol Tartrate

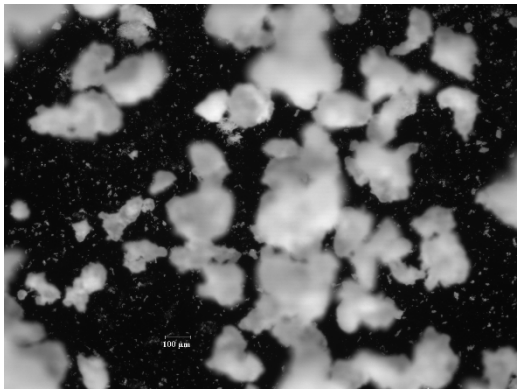


- Grinded - HP
- Grinded - LP
- Cut - HP
- Cut - LP
- Milled - HP
- Milled - LP
- Physical Blend
- Gel
- API

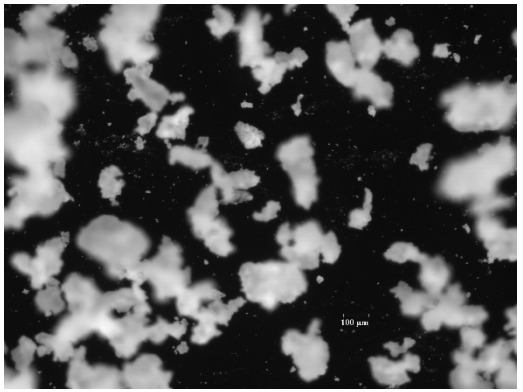
HP = High Porosity Tablet
LP = Low Porosity Tablet



Cut (5X)



Milled (5X)



Grinded (5X)

Summary

- The field of abuse deterrent formulation is relatively new
  - Fast moving and rapidly evolving
  - New technologies are being developed almost daily
- How products are manipulated can affect results
  - Need to have standard methods of manipulation that are representative of abuser's action in the real world

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