Excipient properties affecting the mechanical performance of abuse deterrent formulations

Development and Regulation of Abuse-Deterrent Opioid Medications – Public Meeting

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Sheraton, Silver Spring, MD

Heather Boyce & Stephen W. Hoag, Ph.D.
NIPTE & UMB-School of Pharmacy
20 N. Pine St.; Baltimore MD 21201
Email: shoag@rx.umaryland.edu

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Outline

- Introduction
- Failure modes
- Risk analysis
- Assessment of factors affecting performance

Goals

- Elucidate and disseminate the scientific principles that underpin the abuse deterrent technologies
  - Use these principles and data to:
    - Conduct a risk analysis of products
    - Assess abuse deterrent performance test methods

Abuse of CR Opioid Dosage Forms

- **Dose dumping via destruction of CR barrier:**
  - **Oral ingestion**
  - **Nasal insufflation**
  - **Smoking**
- **Drug extraction from whole or broken down tablets:**
  - **IV injection**

Abuse Deterrent Strategies

Approach	Example
Agonist-antagonist combinations Sequestered antagonist with Differential bioavailability	 Morphine/naltrexone Buprenorphine/naloxone
Aversive components Aversive oxycodone IR	 Hydrocodone/acetaminophen
Produgs	Lisdexamphetamine
Physical barriers Physical resistance Gel based or gel forming	 Polyethylene oxide matrix oxymorphone ER Polymer matrix embedded oxycodone CR

Most commonly used methods – Focus of talk

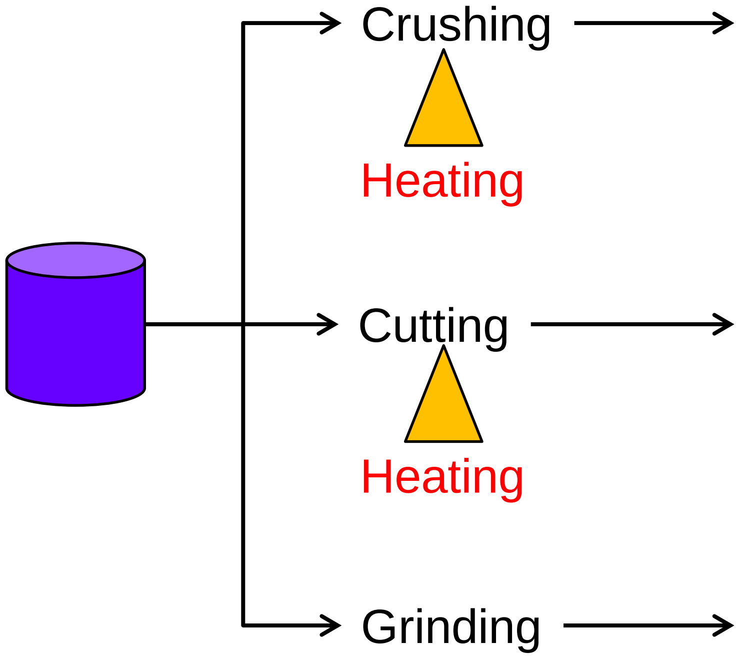
Failure Modes

- **Each abuse deterrent technology has its own failure modes**
- **Physical barriers**
  - **Key failure mode**
    - **Destruction of the barrier**
    - **Ingestion of the drug via route that has rapid uptake**

Covered in Dr. Byrn's lecture

- **Key scientific questions**
  - **What are the critical quality attributes that affect ruggedness of the barrier**
  - **What are the critical quality attributes that affect administration and API uptake**

Failure Modes – Cont.



- Ingest PO
- Snort nasally
- Extract API for injection
- Smoke

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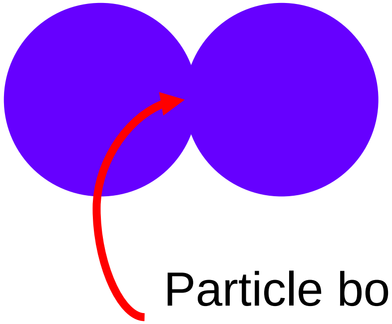
Creating Physical Barriers

- **Tablet Hardness**
  - **Abuse deterrent tablets have crushing force greater than 500 N**
    - **Heating during manufacturing creates melted bridges between particles**



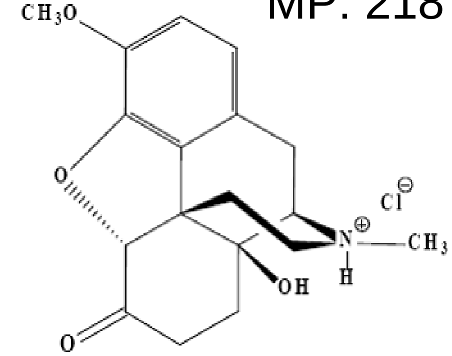
Particle bond formed by polymer melting

- **Liquid syringeability**
  - **When a tablet is placed in water it forms a gel or viscous liquid that cannot be injected**
    - **Viscosity comes from highly viscous polymers**

Physical Barriers in Marketed Products

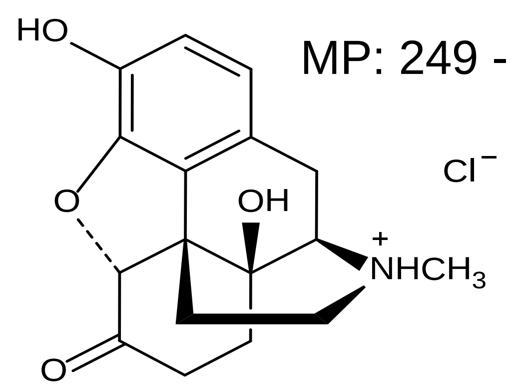
Opana® ER	OxyContin® OP
API: Oxymorphone HCl	API: OxyCodone HCl
Polyethylene oxide	**Polyethylene oxide**
Hypromellose	**Hypromellose**
Alpha-tocophenol	Butylated Hydroxytoluene
Magnesium Stearate	Magnesium Stearate
Polyvinyl alcohol	----------
Polyethylene glycol	Polyethylene glycol 400
Titanium dioxide	Titanium Dioxide
Marogol	----------
Talc	----------

MP: 218 - 220°C



Oxycodone HCl

MP: 249 - 250°C



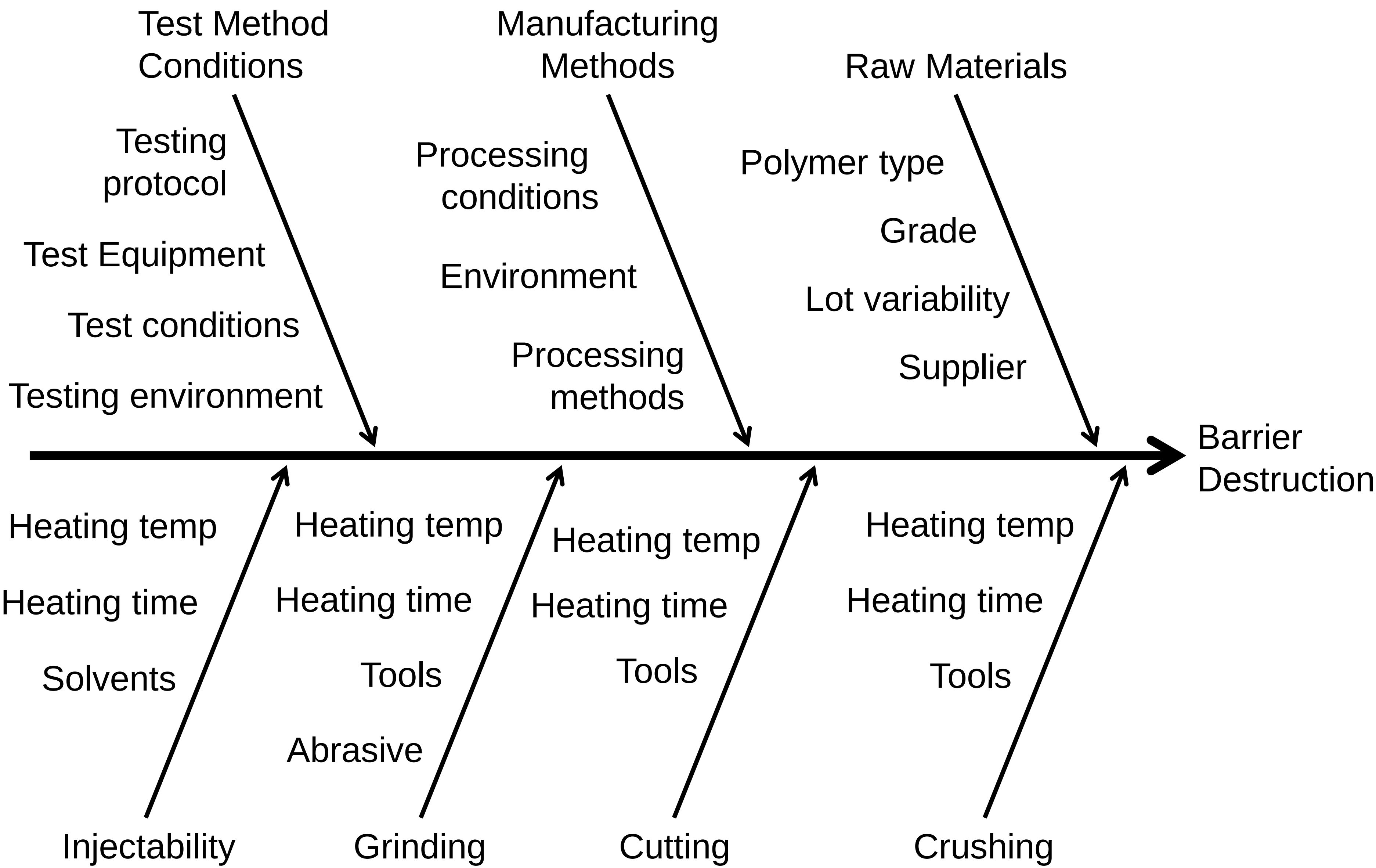
Oxymorphone HCl

Finding: Solid State Key to Performance

- **Dosage form solid state formed by:**
  - **Amount of heating and shear → affects**
    - **Porosity**
    - **No. of bridges**
    - **Degree of polymer crystallinity**
    - **Degree of drug incorporation into polymer**

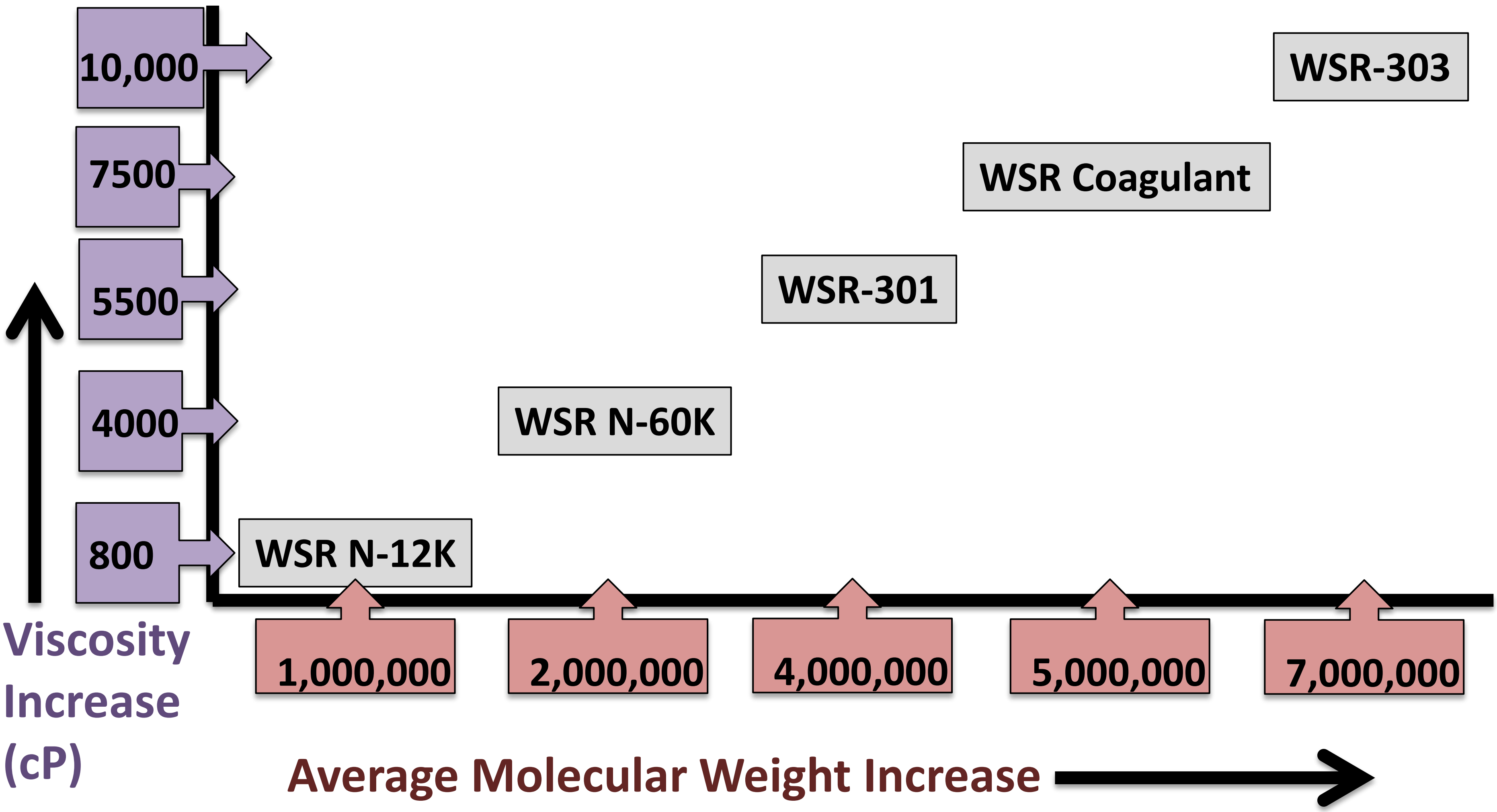
  Tablet hardness
- **Ruggedness dependent upon solid state**
  - **Rate of polymer breakdown during heating**
    - **Loss in tablet hardness upon heating**
    - **Loss in viscosity**

Mechanical Failure Modes



Variation—Grades of PEO

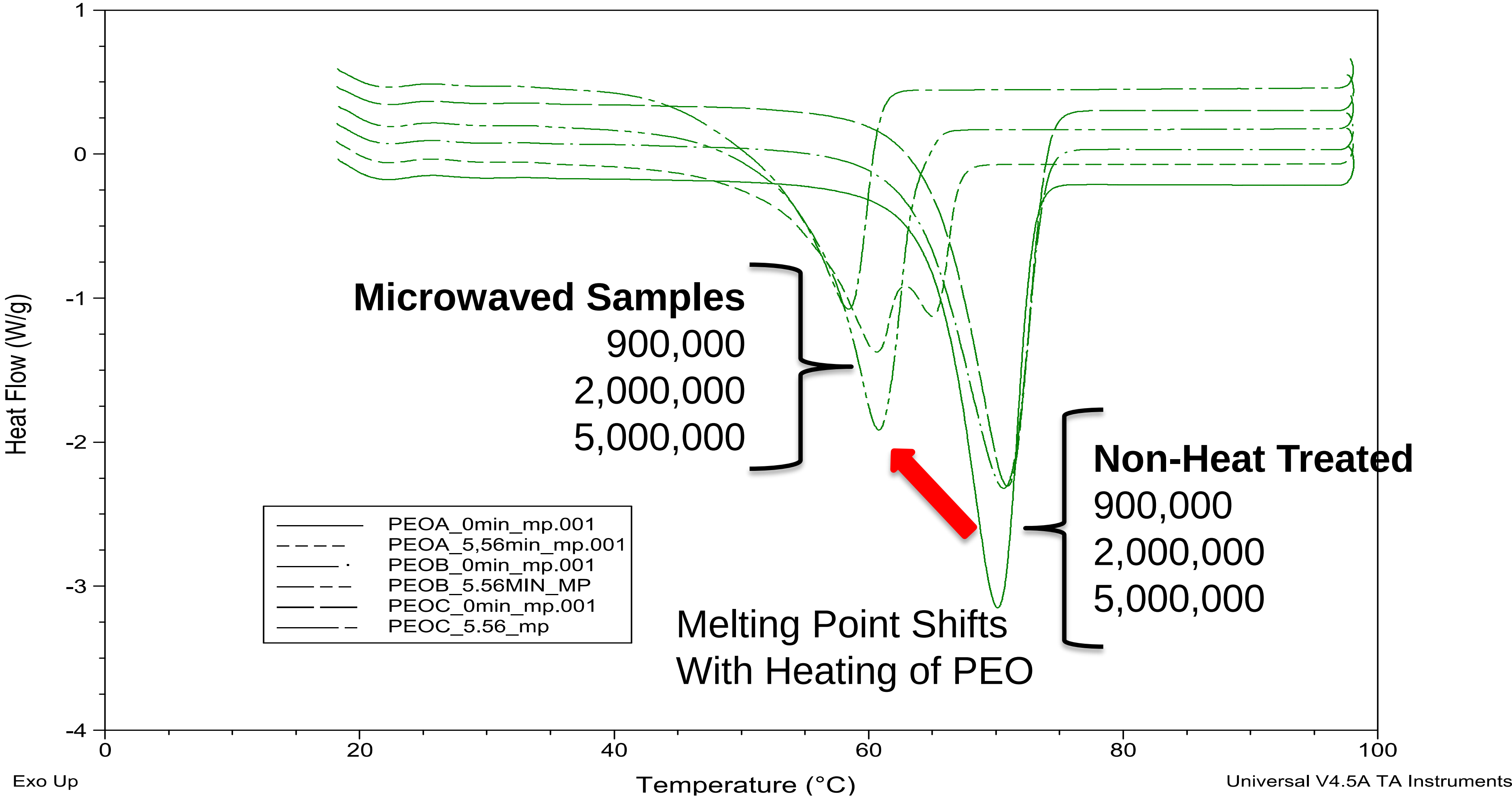
DOW Chemical – High MW grade PEO



Polyox Water Soluble Resins. Dow Chemical Literature

Thermal Behavior of Neat Polymers

Distinctive Endothermic Event for PEO:
Differential Scanning Calorimetry (DSC)



Sintering vs Hot Melt Extrusions

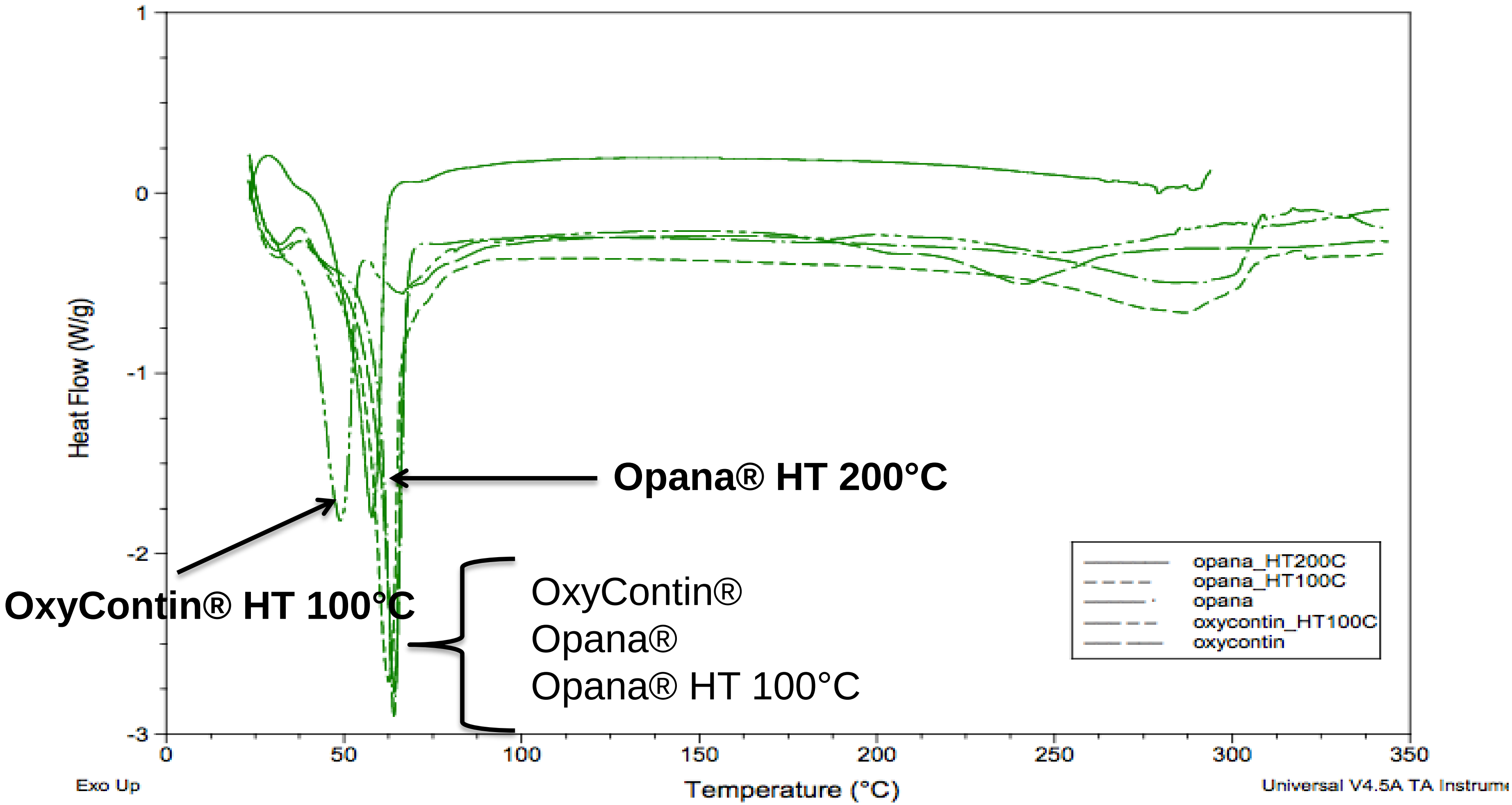
Blend
↓
Compress
↓
Sinter

Blend
↓
Hot Melt Extrusions
↓
Compress

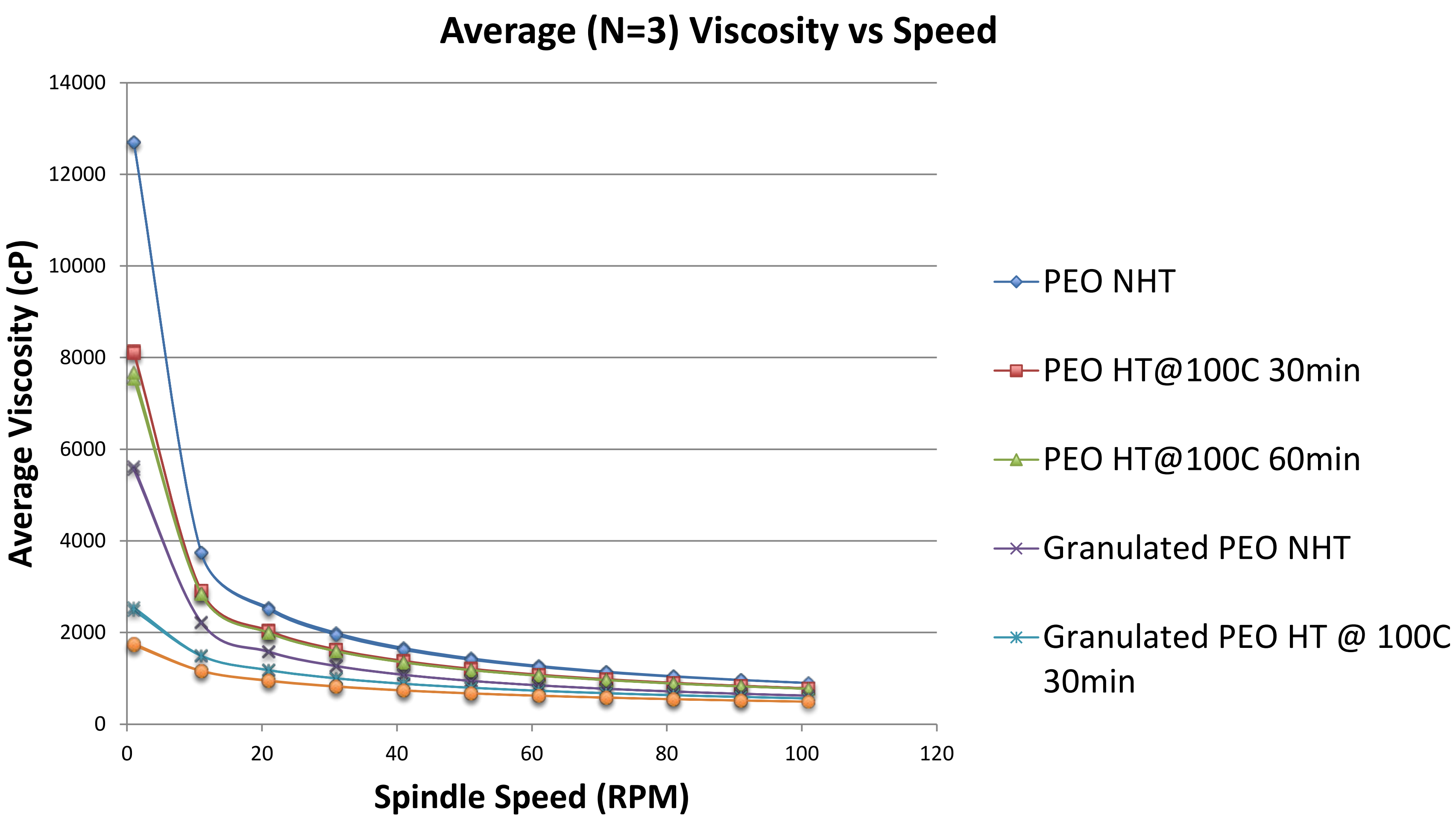
Sintering elevated temp for long time, but no shear

High shear mixing at elevated temperature

Thermal Behavior of Drug Product



Viscosity of 2million MW PEO



Summary

- For physical barrier methods
  - Assessment of solid state is key to understanding performance
    - Grade of PEO
    - Manufacturing shear, i.e. production method
    - Manufacturing heating temp. and time