Foundations of In Vitro Comparisons of Generic Opioids to Reference Listed Drugs (RLDs) with Labeling Describing Abuse-deterrent (AD) Properties: FDA's Research Effort

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Outline

- FDA experience with abuse-deterrent (AD) formulations
- General considerations for in vitro method development
- FDA's research work on product and process understanding related to AD properties

FDA Work to Support the Science of Abuse-Deterrent Formulations

To understand these novel and complex formulations, we have developed infrastructure:

- Manufacturing science equipment installation and training
- Analytical and characterization equipment and training
- Hiring of staff with formulation and manufacturing science background and training
- Dedicated research programs to evaluate complex material (excipients), process selection and their impact on in vitro AD performance
- Engaged in review and policy

Lessons Learned…

Based on the generic guidance:

- When reference listed drug (RLD) product has abuse deterrent properties described in its labeling:
  - Test product is expected be no less abuse deterrent than RLD
  - With respect to all potential routes of abuse
  - Using comparative in vitro approaches

Translation of the scientific knowledge…

Sufficient product and process understanding is critical to:

- Mechanistic understanding of the design of abuse-deterrent properties to help identify the *strength* and *failure mode* of the RLD and test product
- Develop suitable methods for the purpose of comparison
- Understanding formulation and process variability and their potential impact on abuse-deterrent performance

General Considerations for In Vitro Comparative Studies

The challenge: complexity of the design

A possible scenario:

- Minimal of two comparators (reference, test)
- Minimal of two forms of sample (intact, compromised)
- With more than a dozen possible methods to achieve a desired manipulation outcome (e.g. compromise the integrity of the dosage form)
- Minimum of eight different solvents
- Various temperature conditions
- Different volumes
- Different time points

Number of experiments goes into thousands (2x2x12x8x2x3x4= 9216)

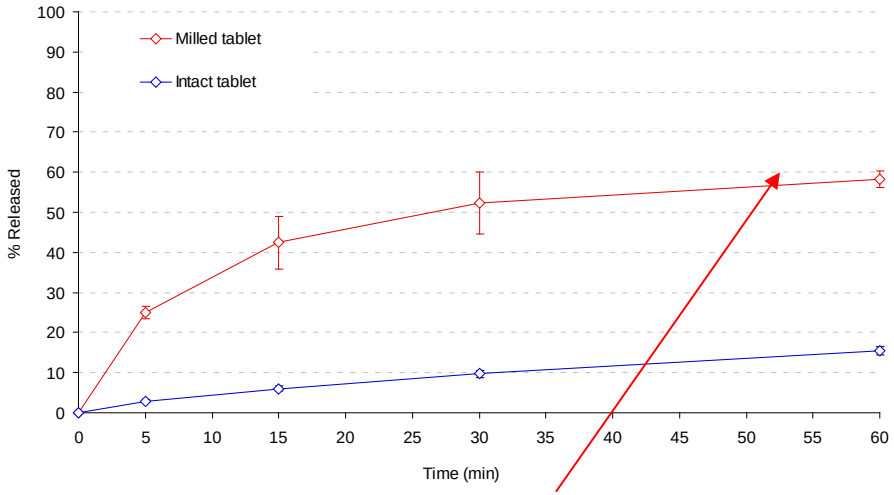
- Battery of tests should not result in data-dumping which burdens both industry and the Agency
- The experimental design should be guided by the understanding of the ADF design mechanism and failure mode of the RLD product

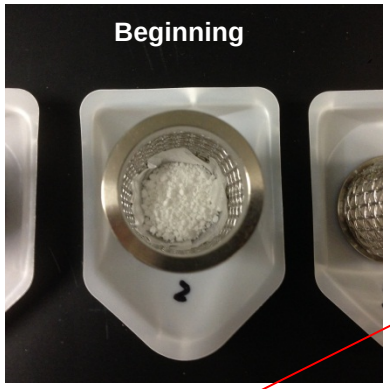
Method Development Considerations, cont.

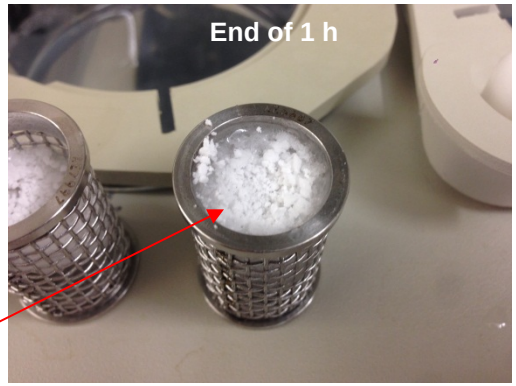
Suitability of a product release method for in vitro abuse-deterrent evaluation should not be assumed

For example:

- Manipulated dosage form floats (USP 1&2) and prevent auto-sampling (USP 2)
- Variations and incomplete release (USP 1&2)







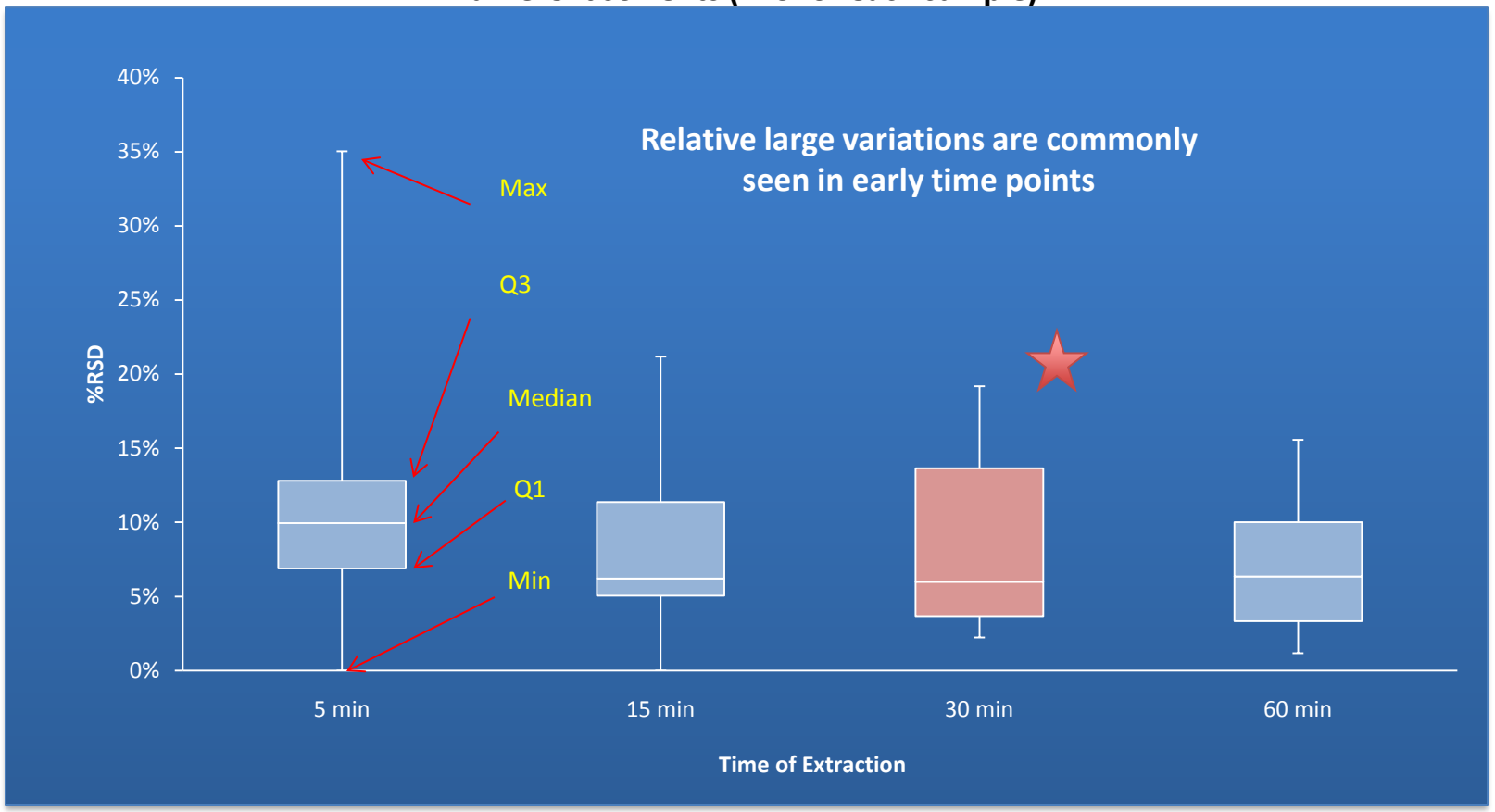
Rapid gelation of PEO prevents further water penetration and delay drug release/extraction

FDA generated data (not published), using sotalol as surrogate

Method Development Considerations, cont.

The variation (relative standard deviation, %RSD) is similar to typically seen in a validated analytical method, or justified statistically for point of comparison

Summary of extraction data for various manipulated dosage forms: 3 manipulation conditions, 11 different solvents (n=3 for each sample)



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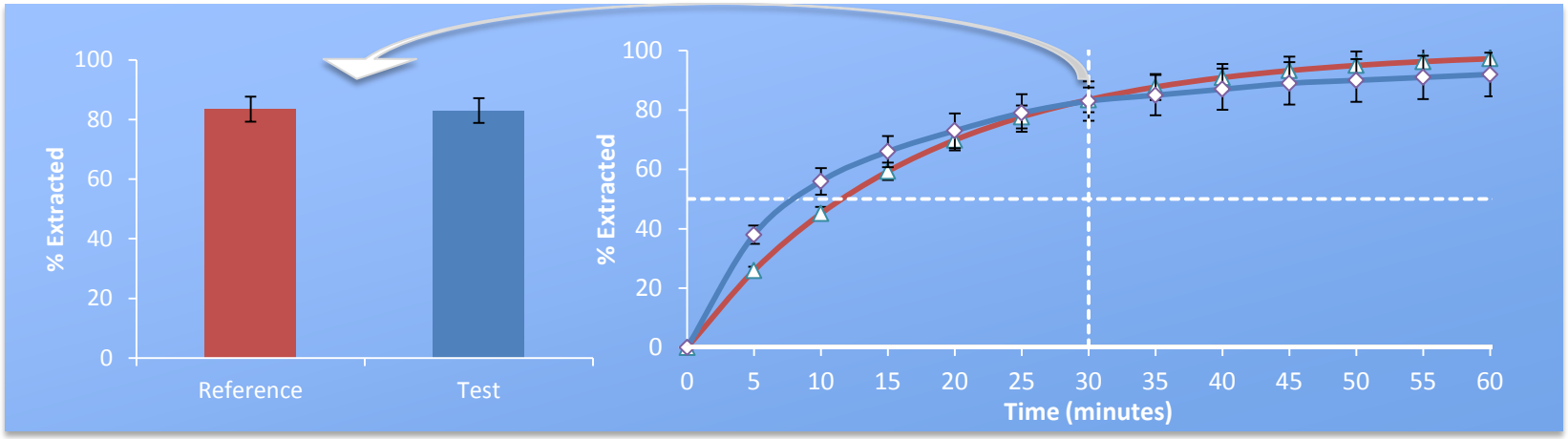
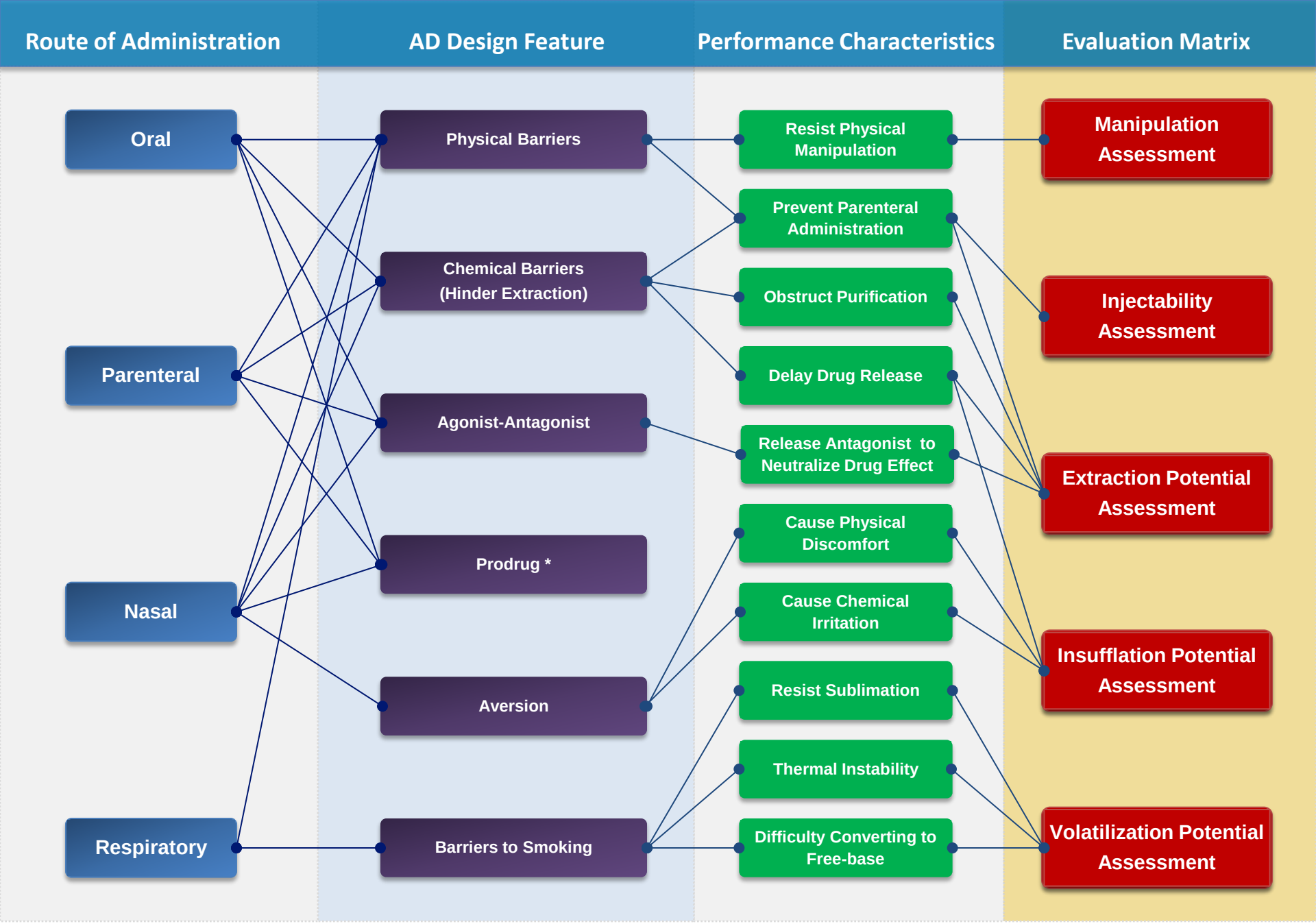
Method Development Considerations, cont.

During method development, important details include:

- Extraction% as a function of time: profile of extraction/dissolution (time points)



- Temperature selection: material properties driven
- Solvent selection: commonly available ones, e.g. water, ethanol, etc. plus potentially relevant ones
- Sample repetitions: n>3
- Volume: 1 mL - **10 mL - 100 mL** (the sink-conditions?)

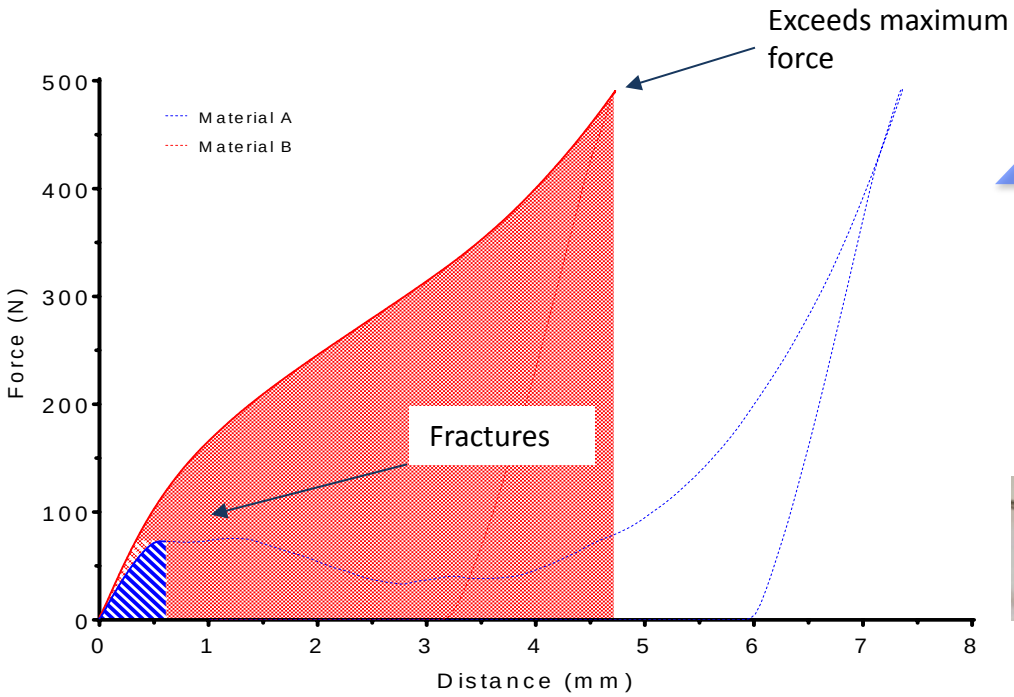


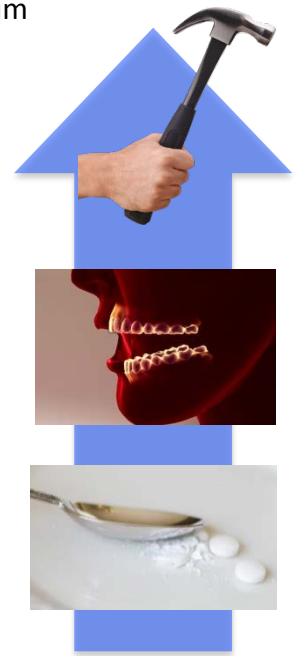
X. Xu, A. Gupta, M. Al-Ghabeish, S.N. Calderon, M.A. Khan, Risk based in vitro performance assessment of extended release abuse deterrent formulations, International Journal of Pharmaceutics, 500(1–2), 2016, pp. 255-267

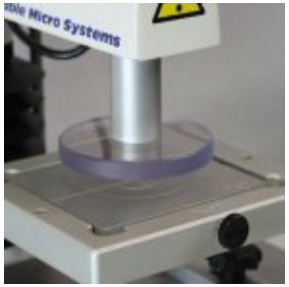
Resist Physical Manipulation (against grinding)

FDA generated data (not published), using sotalol as surrogate

Resist Physical Manipulation --> Tablet Hardness --> Force Displacement



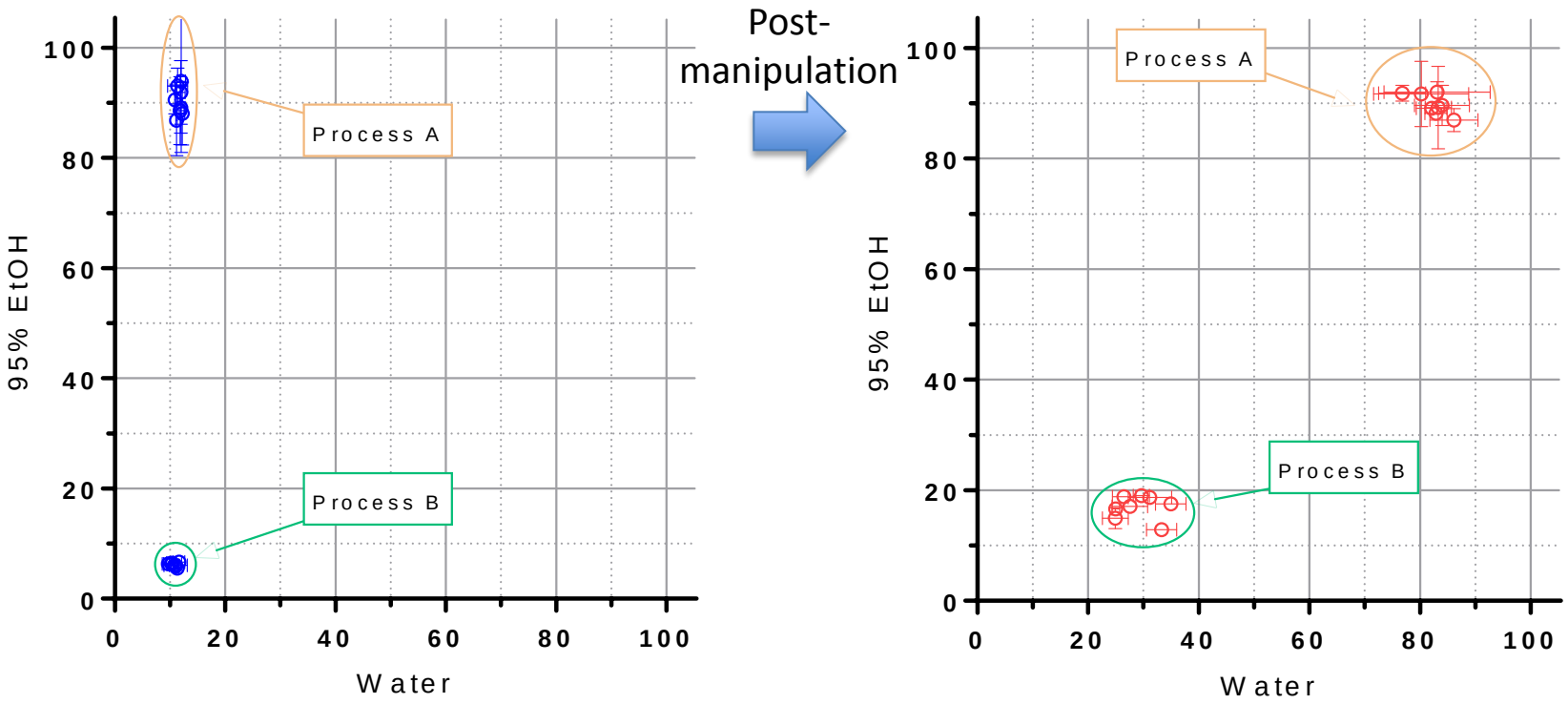




Z. Rahman, et al. Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations, International Journal of Pharmaceutics, 502(1–2), 2016, pp. 138-150

Impact of Process on Abuse-Deterrent Properties

AD properties may not be inherently stable, and knowledge of process impact can reduce the risk of product failure (beyond typical efficacy and safety)



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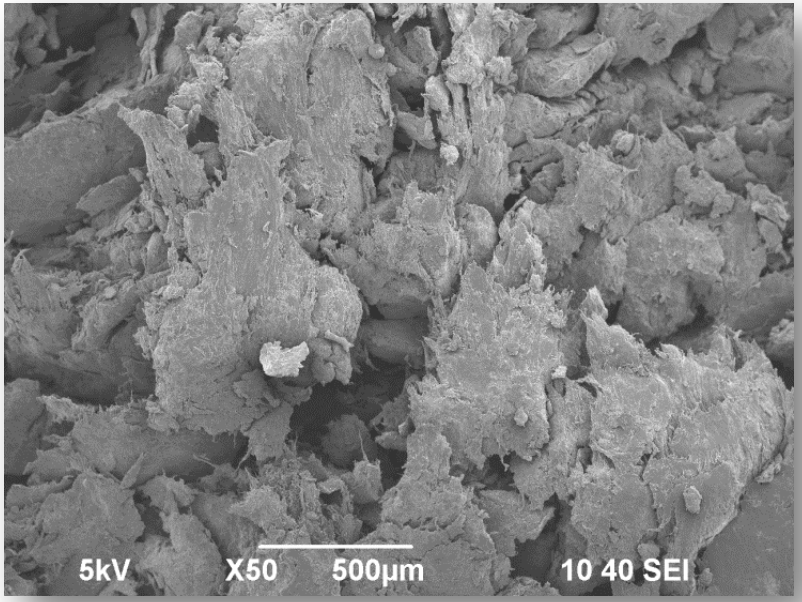
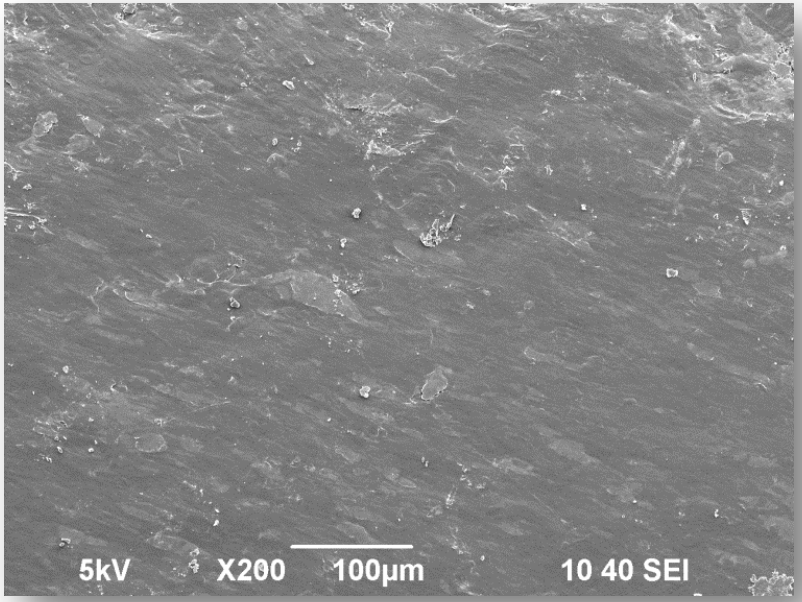
Impact of Process on AD Properties: Mechanism

Tablet formed from Process A



Tablet formed from Process B



Higher porosity observed in tablets formed from Process A leads to significant capillary action of the solvent. Additionally, due to relatively low compressibility, tablets do not have sufficient physical strength as compared with the ones formed from Process B.

FDA generated data (not published), using sotalol as surrogate

In Vitro Abuse-Deterrence Method Verifications

- Do the methods clearly define the ability of the formulation to prevent abuse?
  - Laboratory Manipulation and Extraction Studies
    - Sample manipulation for inhalation or injection (crushing, splitting, grinding, heating, etc.)
    - Extraction and solubility studies (various solvents)
    - Effects of time, temperature, pH, and agitation on solvent extraction
    - Particle size distribution
    - Syringeability
- Do the methods provide stability information for the drug substance and drug product?
- Do the methods provided adequately evaluate the drug substance, drug product, and possible impurities/degradants?

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

Summary

- ADF testing to date has been non-standard, making comparison and overall assessment challenging
- To support the development of products with AD properties, FDA has committed resources for research on manufacturing science and in vitro standards in FDA and National Institute of Pharmaceutical Technology and Education (NIPTE) laboratories
- AD properties can be defeated with varying degree of difficulty; and hence iterative improvements on the existing abuse-deterrent technology and/or more innovative designs are needed
- Appropriate in-vitro assessment of AD properties is critical: it should be risk-based using knowledge of product and process understanding , and performed within the context of its intended use.

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