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Microstructural Techniques for Demonstrating Bioequivalence in Dry Powder Inhalers

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Regulatory basis for an alternative to clinical endpoint BE

An addition to the 2003 Federal Drug and Cosmetic Act, section 505(j)(8)(A)(ii) indicated that:

"For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by ***scientifically valid measurements*** *intended to* ***reflect the rate and extent*** *to which the active ingredient or therapeutic ingredient becomes available at the site of action."*

FDA has introduced the concept of microstructural (Q3) equivalence to address these measurements for locally acting products.

What is Q3?

Classify product similarity:

Q1

Same components

Q2

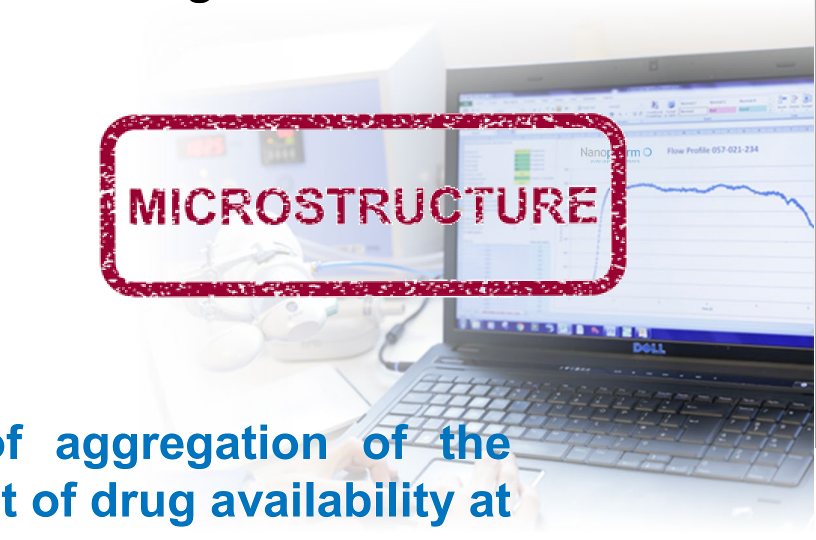
Same components in the same concentration

Q3

Same components in same concentration with the same arrangement of matter

Microstructure Determination by Integrated Dissolution:

- In vitro Dissolution
- In Vitro Release Testing
- State of aggregation by MDRS



These validated in vitro orthogonal methods investigate the state of aggregation of the formulation, which can be used as input to predict the local rate and extent of drug availability at the sites of action and to systemic circulation

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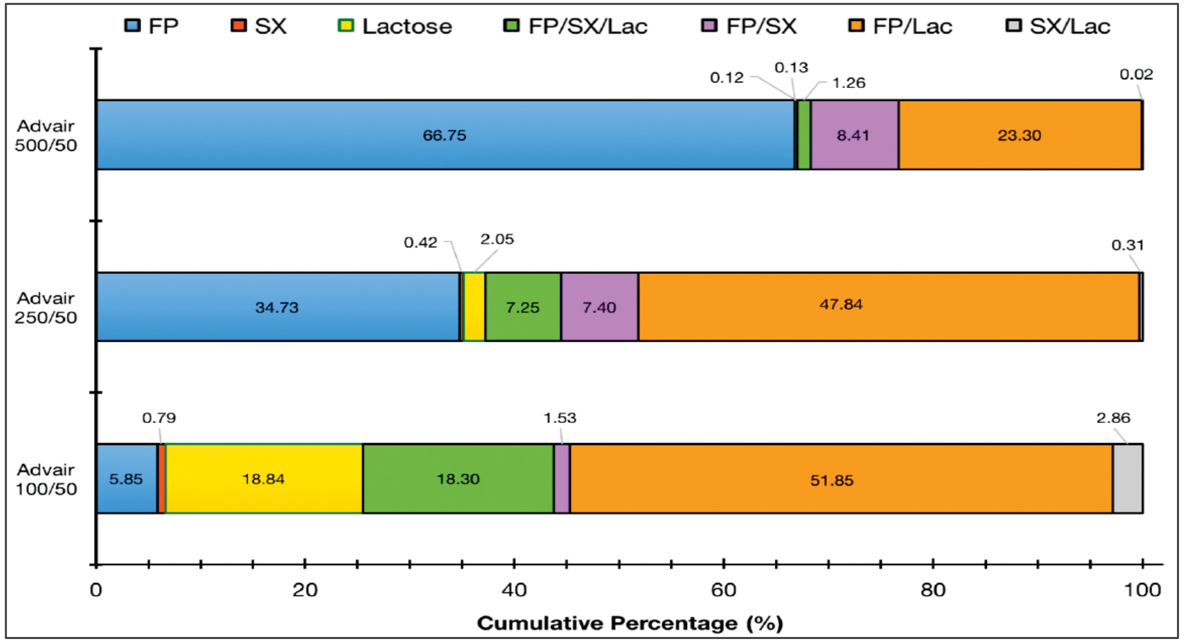
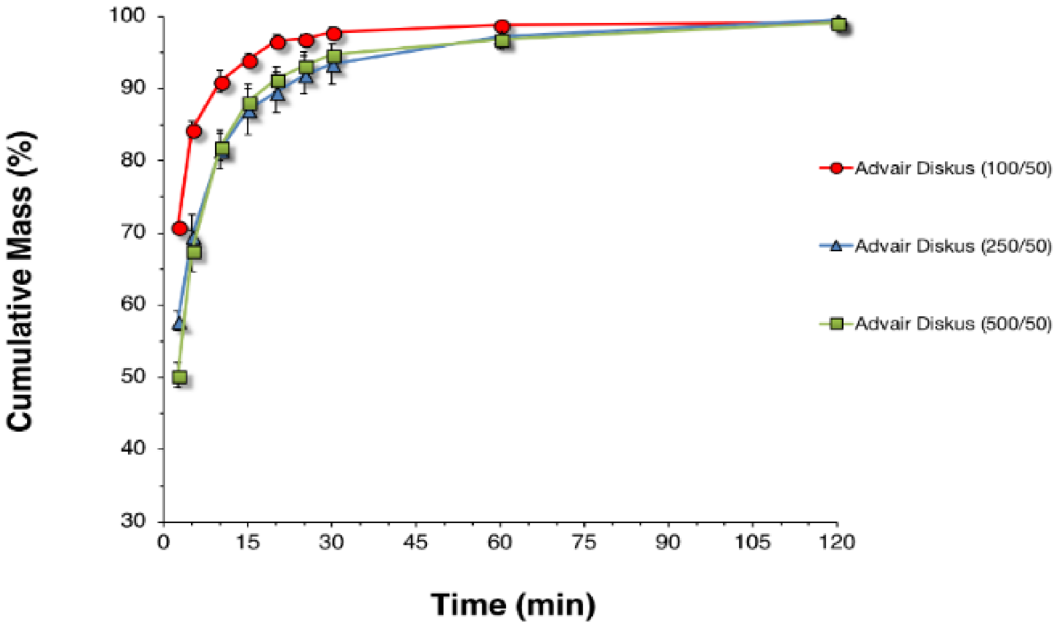
In Vitro Dissolution and MDRS for FP (dissolution rate limited API)



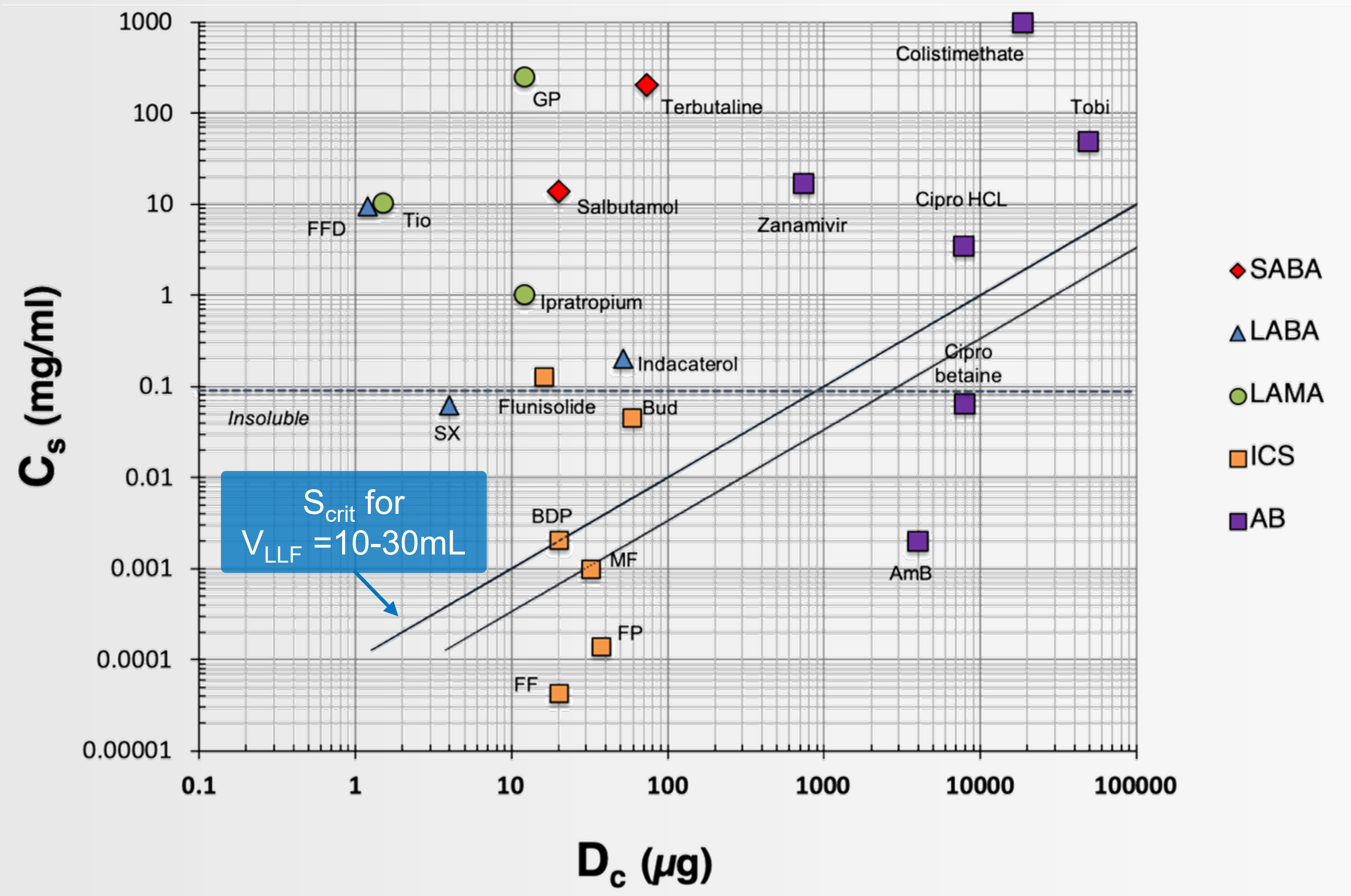


- **Dissolution rate of FP DPI is different** for the three strengths
- There is also a noticeable **difference in microstructure** as determined by MDRS
- e.g. **less free FP** in 100/50 strength Advair vs. 250/50 and 500/50 → **faster dissolution** of 100/50

Qualitatively and quantitatively (Q1/Q2) equivalent products may not be microstructurally (Q3) equivalent

Farias, G., et al. (2024). Microstructural Characterization of Dry Powder Inhaler Formulations Using Orthogonal Analytical Techniques. *Pharmaceutical Research*.

Limited number of APIs are dissolution rate limited



- Dissolution-limited absorption is only important for a small number of APIs.
- An IVRT system would be required for non-dissolution limited APIs.
- Both systems require a validated aerosol collection apparatus of the ISM.

Hastedt, J., et al. (2016). Scope and relevance of a pulmonary biopharmaceutical classification system AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD. *AAPS Open*, *2*(1).

Difference between Dissolution and Release

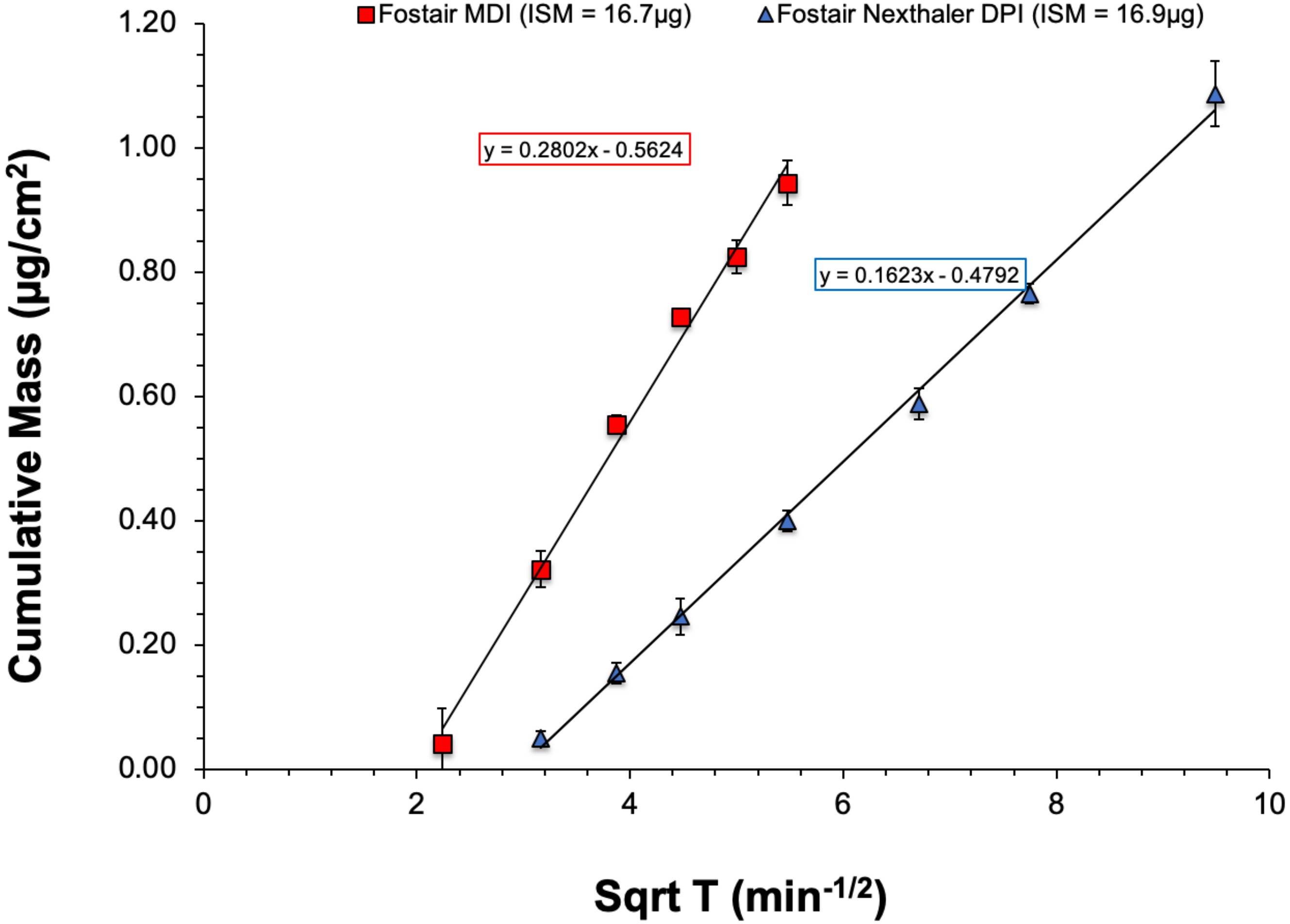
Drug Dissolution Process

1. Wetting of the particle surface.
2. Breakdown of solid-state bonds.
3. Solvation of the molecules
4. Diffusion through the boundary layer
5. Convection within the stirred receptor medium

Drug Release Process

1. Wetting and penetration of membrane with receptor media
2. Drug dissolution in limited layer of media
3. Diffusion of solvated molecules through synthetic membrane
4. Diffusion driven by concentration gradient

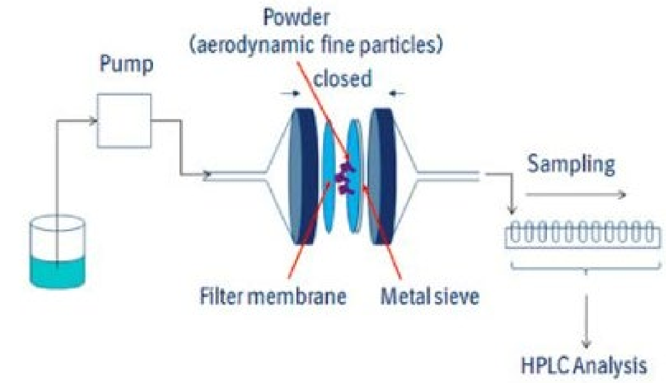
IVRR of EU BDP Fostair MDI and DPI

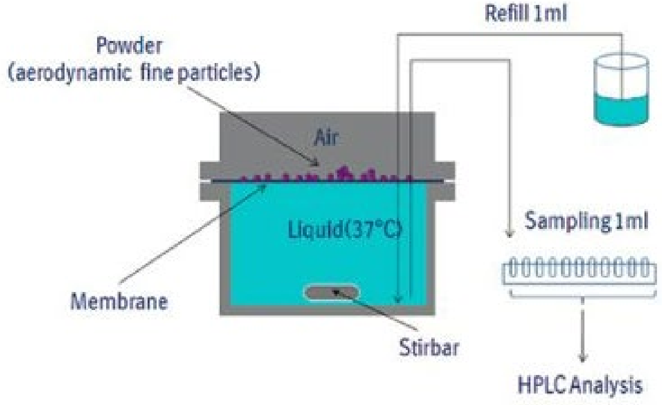


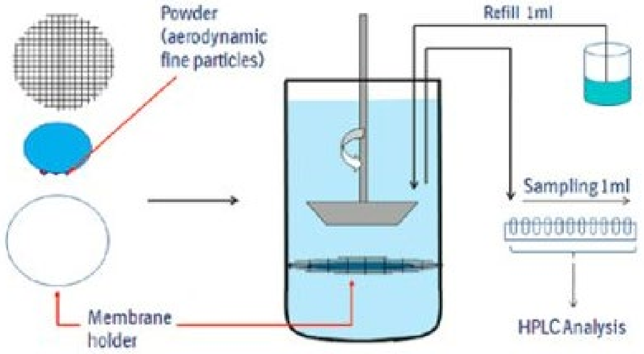
Higuchi plot of the differences in the IVRR of BDP from a Fostair 100/6 solution MDI and a Fostair 100/6 NEX

Price, R. (2020). *Nanopharm-Developing-an-In-Vitro-Dissolution-and-Release-System-for-OIDPs*. 40–44. www.ondrugdelivery.com

IVRT System Comparison







	Flow Through Cell (DissolvIt, Inhalation Sciences)	Franz Cell (RespiCell, University of Parma)	Paddle Apparatus (Nanopharm's IVRT)
Handling	◐	◐	●
Duration of experiment	●	◐	◐
Amount of dissolution medium	●	○	○
Reproducibility	○	●	●
Discrimination power	◐	◐	◐

● → ◐ → ○

Good **Poor**

Sonvico, F., et al,. (2021). Respicelltm: An innovative dissolution apparatus for inhaled products. *Pharmaceutics*, *13*(10).

Gerde, P., et al. (2017). DissolvIt: An in Vitro Method for Simulating the Dissolution and Absorption of Inhaled Dry Powder Drugs in the Lungs. *Assay and Drug Development Technologies*, *15*(2), 77–88.

Salama, R., et al. (2008). Preparation and characterisation of controlled release co-spray dried drug-polymer microparticles for inhalation 2: Evaluation of in vitro release profiling methodologies for controlled release respiratory aerosols. *European Journal of Pharmaceutics and Biopharmaceutics*, *70*(1), 145–152.

Price, R. (2020). Nanopharm-Developing-an-In-Vitro-Dissolution-and-Release-System-for-OIDPs. *40–44. www.ondrugdelivery.com*

May, S., et al. (2012). Dissolution Techniques for In Vitro Testing of Dry Powders for Inhalation. *Pharm Res 29:2157–2166.*

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Take Away Message

- The current guidance does not require dissolution/release data for fast dissolving drugs.

- Generic drug developers are seeking an in vitro lung dissolution/release approach that could improve the reliability of in vitro–in vivo correlation (IVIVC) assessments.
  - Currently, there is no stated recommendation on the method to use from regulatory agencies.

- An IVRT system can be a very valuable development tool for DPIs (i.e. support identifying differences in excipients, manufacturing process, etc.).

- Should IVRT be added to DPI generic programmes?
  - Relevance is molecule specific – not all products need the same tests.
  - Different methods may be suitable to study IVRR – lack of standardisation allows for more flexibility in research
  - Clear guidance needed on IVRT validation

- Further research needed to define IVRT's role in supporting Q3 structural equivalence.

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Thank you

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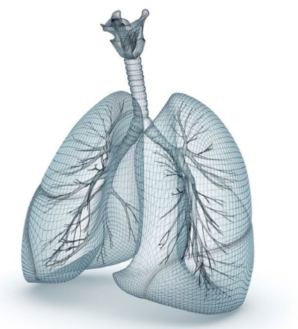

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