Considerations and Challenges for Dissolution Testing of Orally Inhaled Drug Products (OIDPs)

FDA-CRCG Workshop: Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products

Symposium II: Integration of Alternative In Vitro, In Vivo, and In Silico Studies to Establish Bioequivalence of Locally Acting Orally Inhaled Drug Products In Lieu of Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies

Session 1: In Vitro Studies That May Contribute to Alternative Bioequivalence Approaches for Locally Acting Orally Inhaled Drug Products

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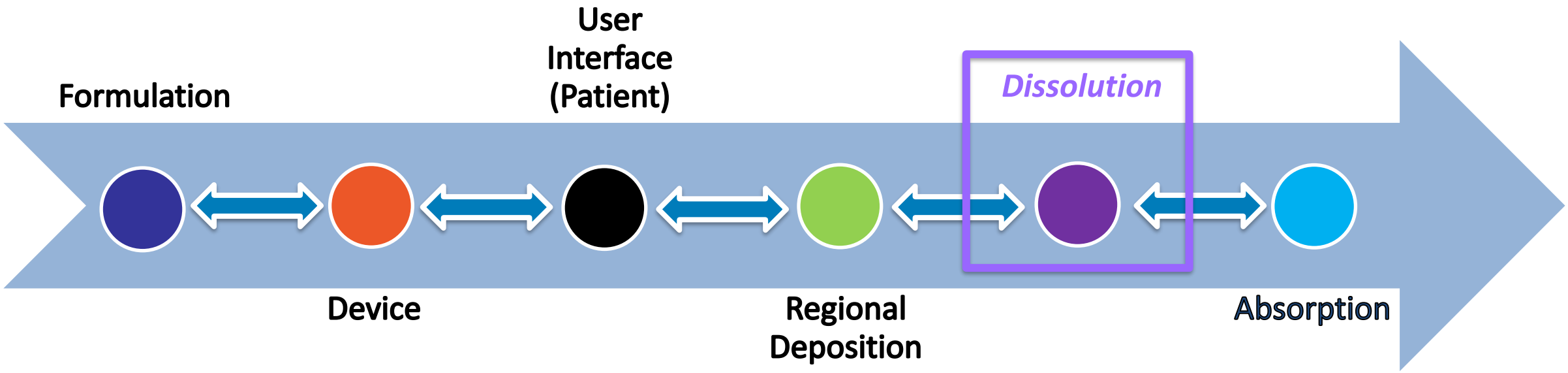
Challenges in Establishing BE for Locally Acting MDIs and Dry DPIs

- Developing generics for **locally-acting MDIs and DPIs** is challenging because of the ***multiple factors that can influence drug delivery to the site of action.***



In Vitro Product Performance + Patient Factors

 BE: Bioequivalence; MDIs: Metered Dose Inhalers; DPIs: Dry Powder Inhalers

Alternative Approaches to CCEP/PD BE Study

If a generic shows formulation sameness (Q1/Q2) and device similarity to the RLD, additional supportive information ***may*** provide a foundation to help ensure the ***equivalence to local site of action*** (lungs).[1]

More Predictive APSD Testing (representative mouth-throat models and breathing profiles)
- Understand impact of patient variability

Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand droplet size and evaporation process of formulation emitted from the device

Morphology Imaging Comparisons (characterization of full range of residual drug particle sizes)
- Understand residual particle morphology and size distribution of formulation emitted from the device

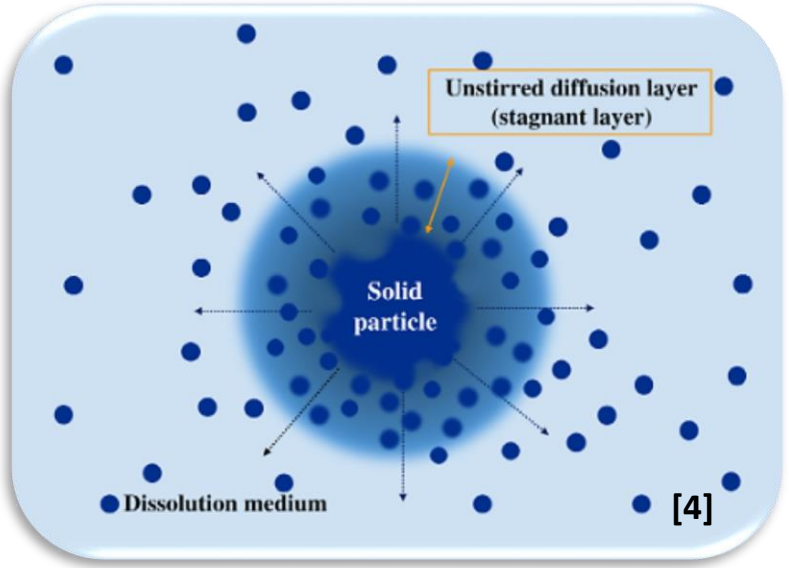
Dissolution
- Understanding how API dissolved at site of action for absorption once deposited

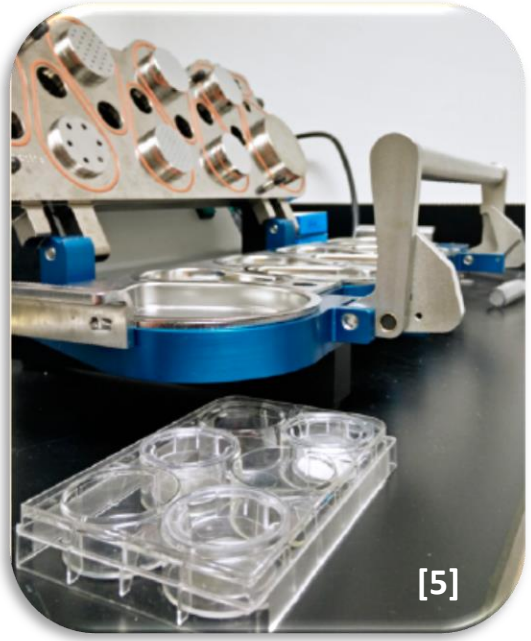
Quantitative Methods and Modeling (e.g., **physiologically-based PK; computational fluid dynamic studies)**
- In vitro-in vivo correlations (IVIVCs; bridge gap between in vitro product performance and regional drug deposition)

Alternative PK BE Studies
- Understanding how PK studies may correlate to in local deposition

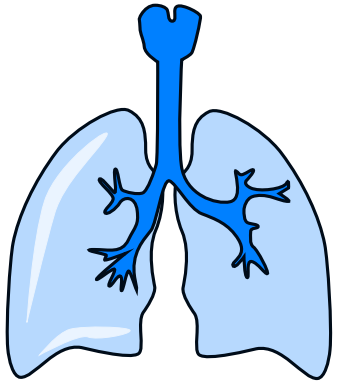
The Role of Dissolution

- **Dissolution:**[2,3] a process by which molecules of a solute (i.e., the drug) are dissolved in a solvent vehicle to understand rate at which drug dissolves.



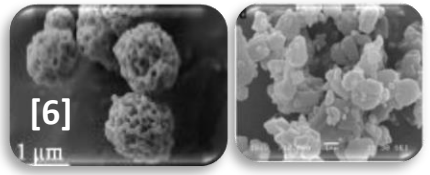


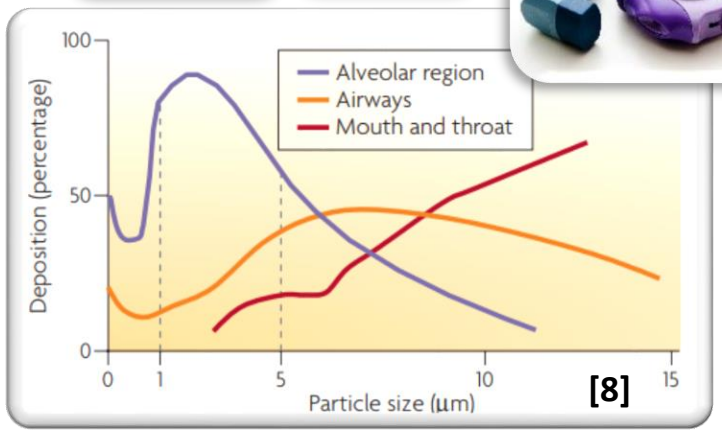
- In the context of inhalation drug products, dissolution may be useful for:[3]
  - ***A product quality control tool***
  - ***BE assessment***
  - ***Establishing in vitro-in vivo correlations (IVIVCs)***
  - ***Input into in silico models***

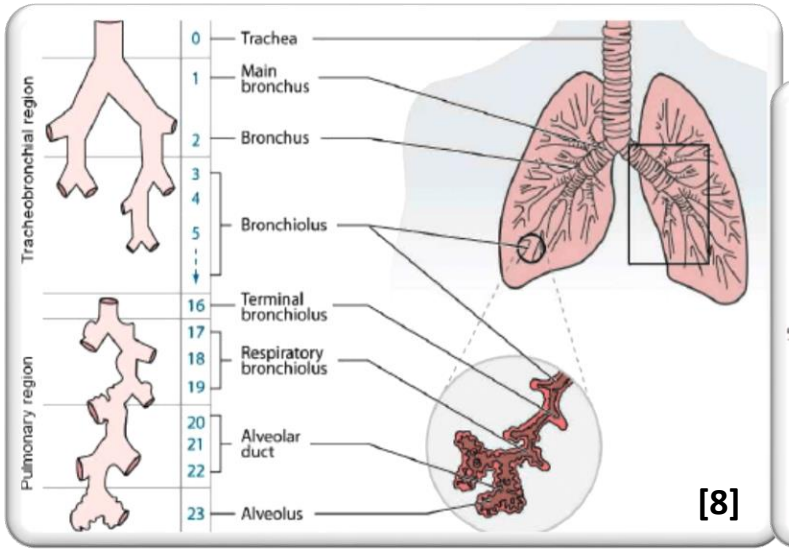


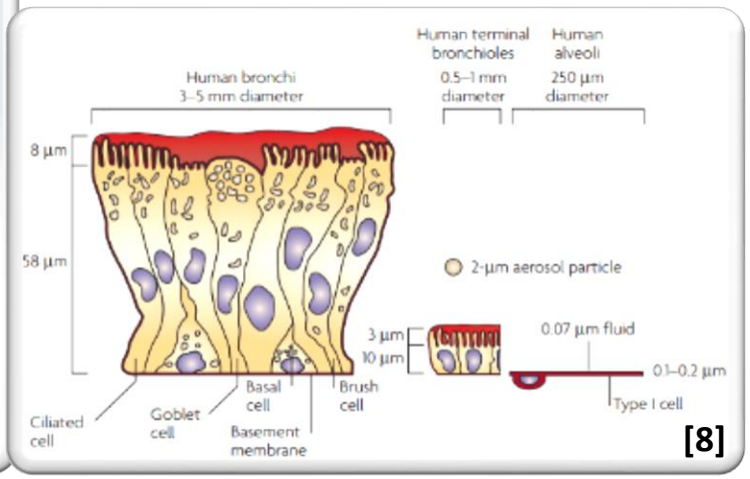
Dissolution in the Context of Inhalation Products

- **Dissolution of inhalation drug products is dependent on:**
  - **Active pharmaceutical ingredient (API) particle size distributions (PSDs) → *Formulation***
  - **Physiochemical properties of the API(s) and excipient(s) → *Formulation***
  - **API(s)-excipient(s) interactions → *Formulation* + *Device***
  - **Region of lung deposition of the API(s) → *Formulation* + *Device* + *Patient Factors***









Challenges and Research Efforts

- **Challenges:**
  - **Lack** of ***standardized*** and ***sensitive*** **dissolution methods for inhalation products**.

- **GDUFA-Funded Research:**
  - **Goal:** Develop an **in vitro dissolution method** for **orally inhaled drug products (OIDPs)** which may be capable of ***predicting in vivo dissolution of drugs*** that are administered via the inhalation route.
    - Gain a better understanding of ***formulation factors*** that impact dissolution, thereby, facilitate potential ***in vitro-in vivo relationships*** of OIDPs.
      - ***Local availability (efficacy)***
      - ***Pharmacokinetics (PK, safety)***
  - **Goal:** Develop a ***quality-by-design (QbD) tool*** for **formulation development** and **product quality control.**

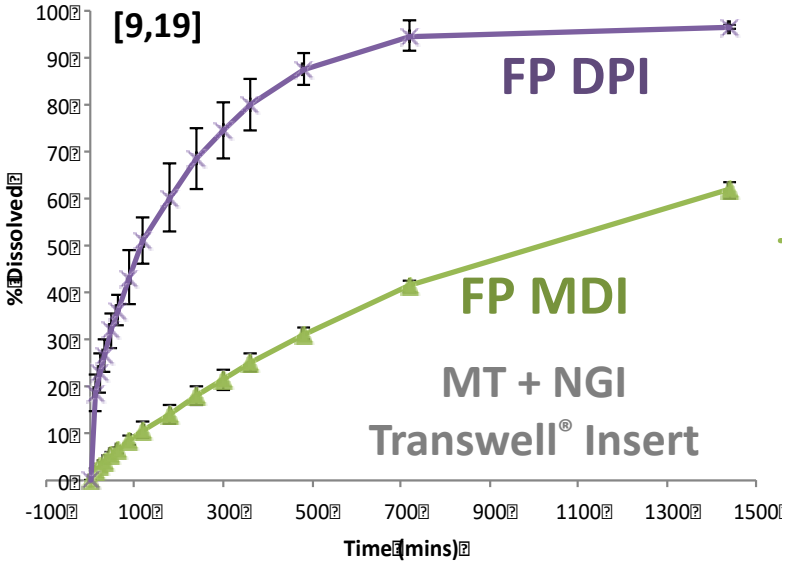
➢ ***Three research grants[9,10,11] (complete) and one contract[12] (ongoing) to develop dissolution methods for OIDPs.***

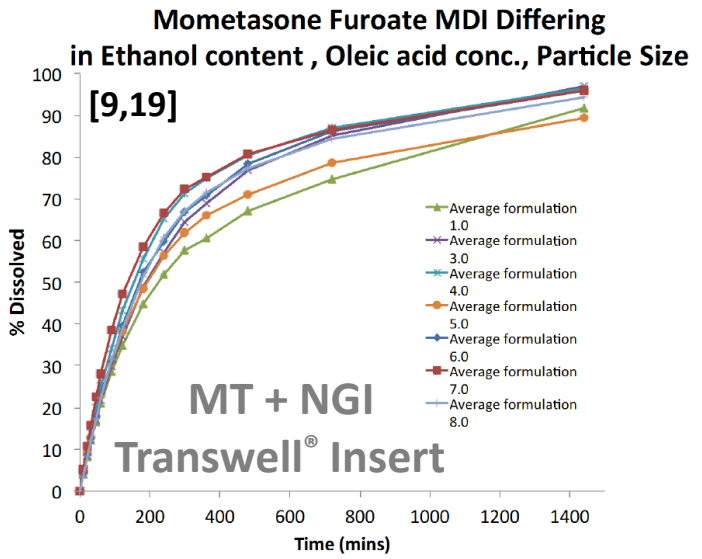
➢ ***One research grant[13] and five research contracts[14,15,16,17,18] (three complete, three ongoing) incorporating dissolution as in vitro method for evaluation of inhalation products.***

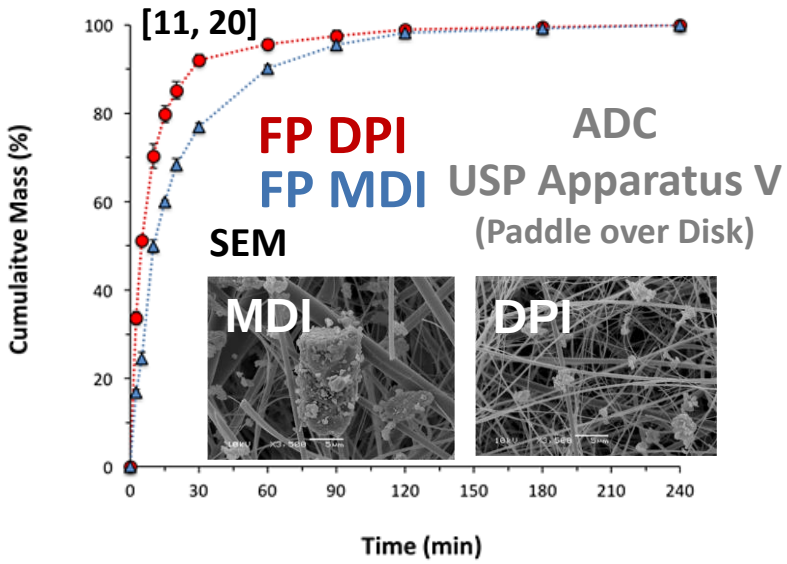
Dissolution and Formulation Differences

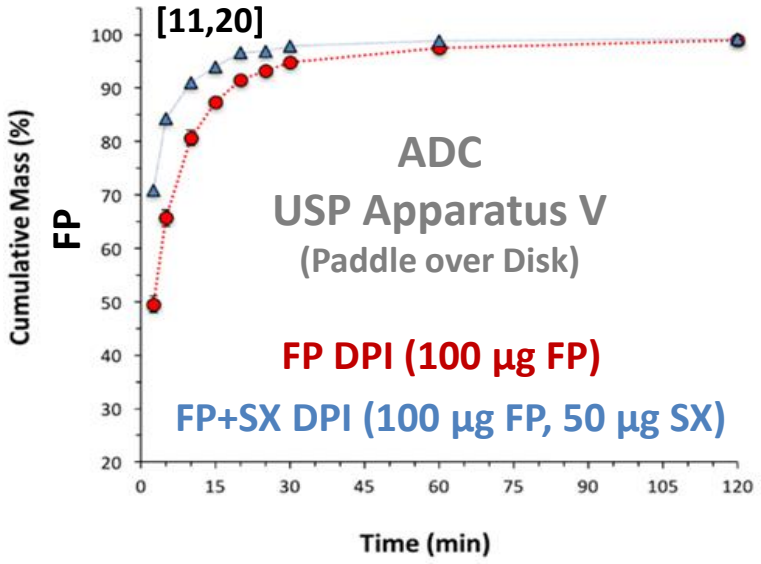
- ***In vitro dissolution is able to capture differences in formulations:***[9,11,19,20]
  - ***MDI vs DPI***
  - ***API particle size and excipient differences***
  - ***Absence/presence of API***

FP: Fluticasone Propionate SX: Salmeterol Xinafoate
MDI: Metered Dose Inhaler DPI: Dry Powder Inhaler
MT: Mouth-Throat Model
NGI: Next Generation Impactor
ADC: Aerosol Dose Collection System



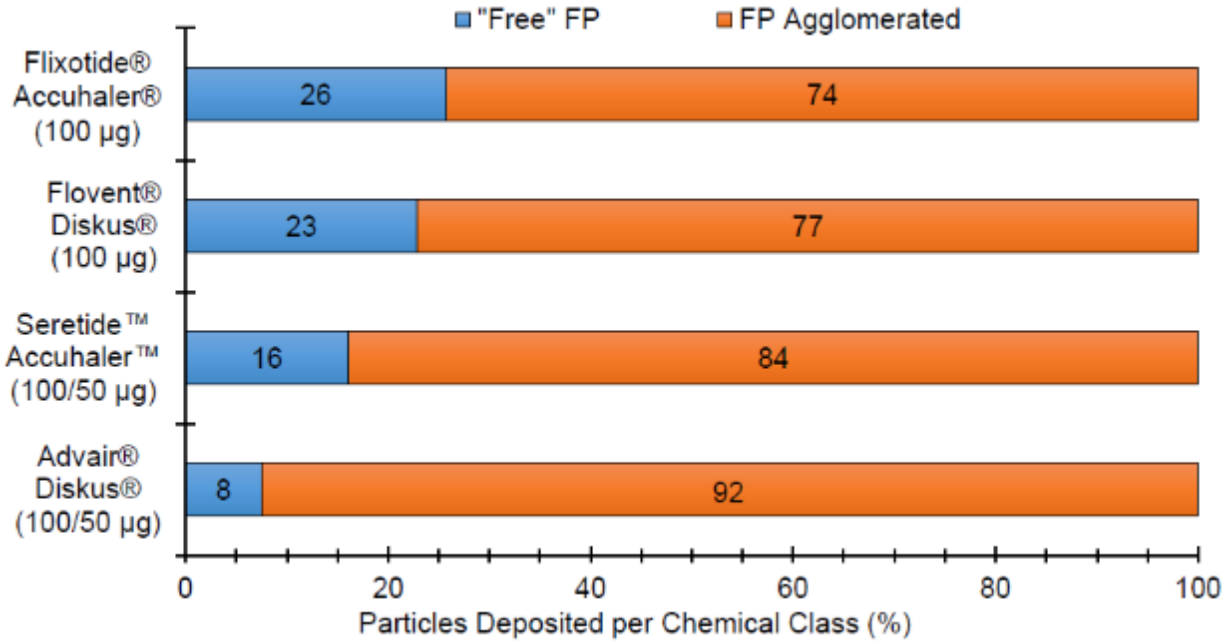


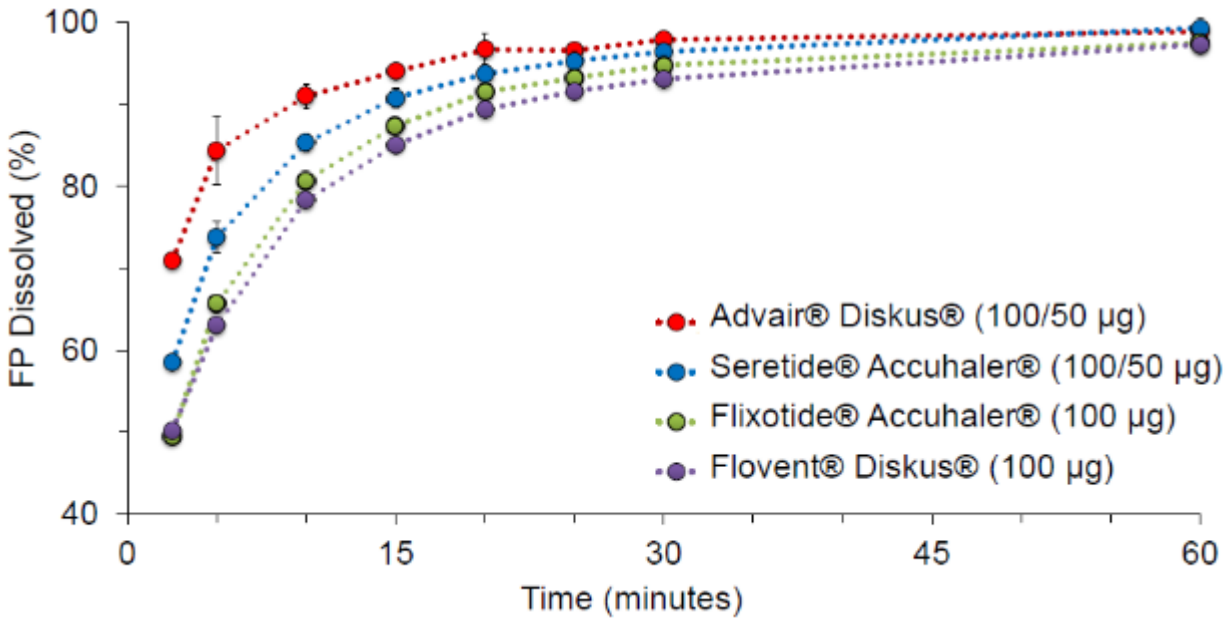




Microstructure and Dissolution

- ***In vitro dissolution is able to capture differences in <u>microstructure</u>.[15,21]***





MDRS of ISM dose collected with ADC system via USP inlet port at fixed flow of 60 L/min, 4 s.

In vitro dissolution modified USP Apparatus V of ISM dose collected from equivalent 500 mcg FP.

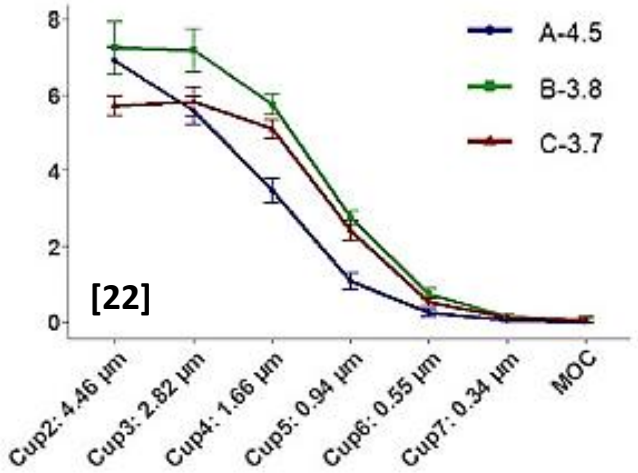
Differences in API, Fluticasone Propionate (FP), agglomerated to the excipient lactose demonstrates difference in dissolution behavior between US and EU marketed products.[15,21]

MDRS: Morphologically-Directed Raman Spectroscopy; ISM: Impactor-sized mass

Dissolution and PK

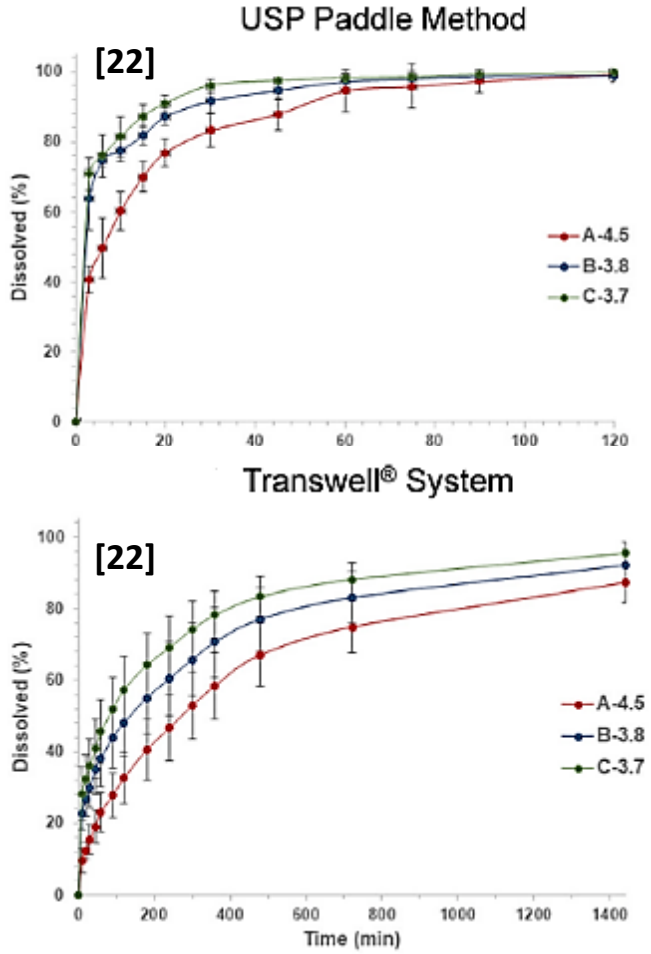
- ***Potential for correlating dissolution to systemic PK.***[9,14,22,23]

- **Fluticasone propionate (FP) DPI Formulations**
  - ***Same API batch (and particle size)***
  - ***Different lactose fines***
  - ***different aerosol performance:***
    - **A: 4.5 µm MMAD**
    - **B: 3.8 µm MMAD**
    - **C: 3.7 µm MMAD**

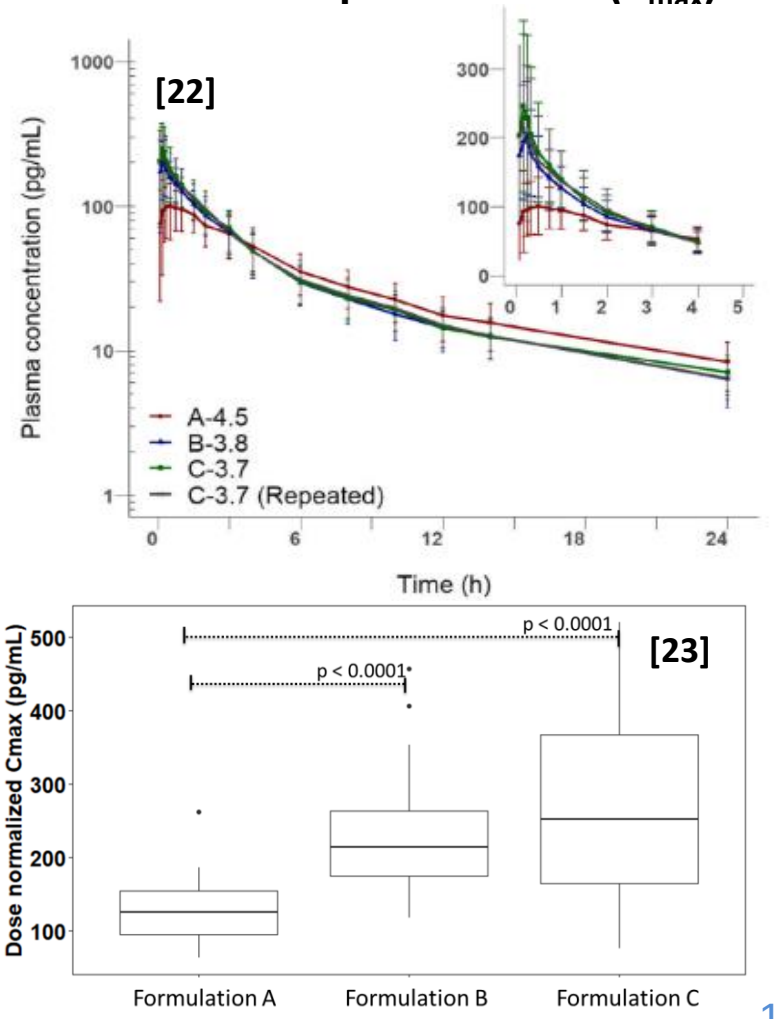


***MMAD**: median mass aerodynamic diameter*
***TLD$_{in\ vitro}$**: amount of drug mass passing through a mouth-throat model*

- **Differences in dissolution behavior of ex-throat fraction (TLD$_{in\ vitro}$).**

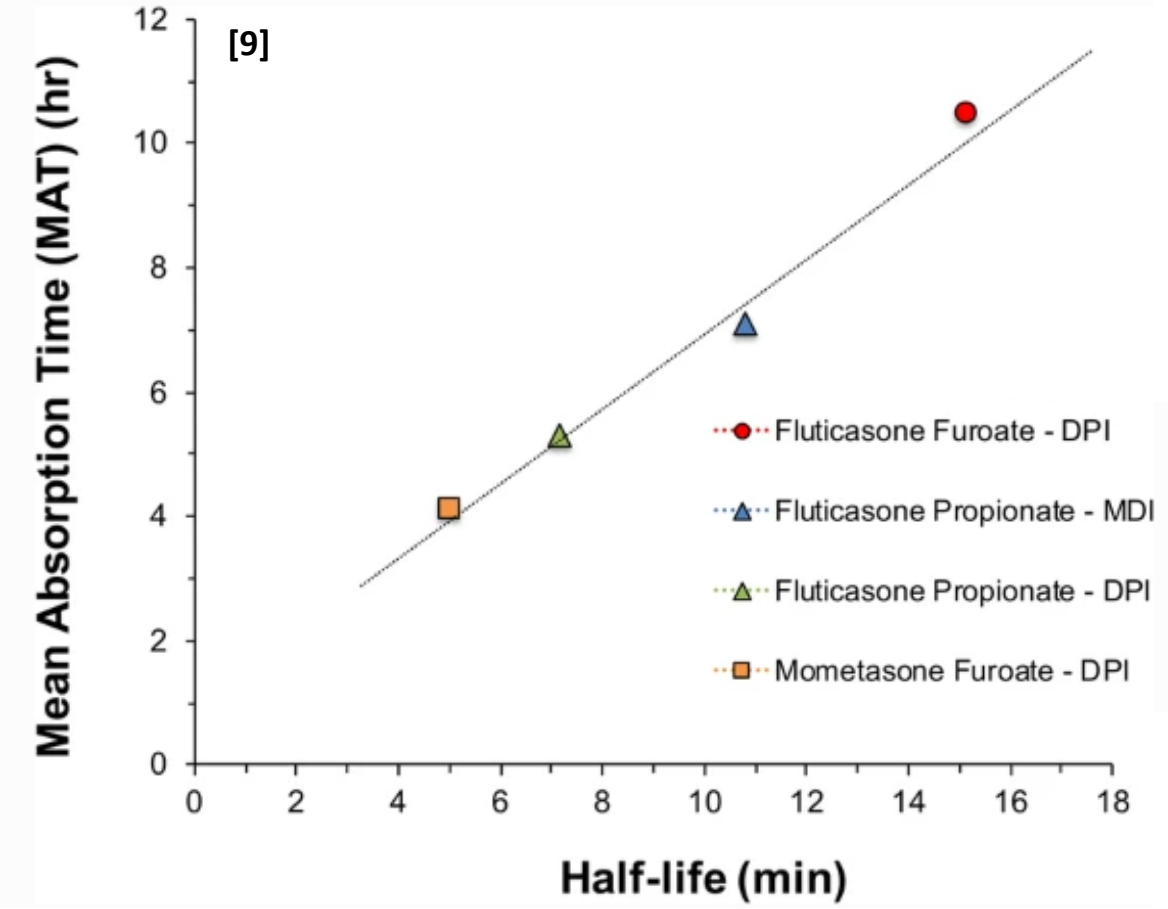


- **Differences PK performance (C_{max}).**



Dissolution and PK

- ***Potential for correlating dissolution <u>to systemic PK</u>.***
  - ***Link mean absorption time (MAT) from PK measurements and dissolution half-life ($t_{0.5}$) for inhaled corticosteroids.[11,20]***



Dissolution Capabilities

- **Lessons Learned**:
  - Developed ***sensitive dissolution methods*** that were capable of:
    - Understanding ***formulation factors*** that impact dissolution.
    - Dissolution can be a ***link between product formulation factors and bioavailability.***
    - Establish ***IVIVCs*** with PK metrics.

Ongoing Questions

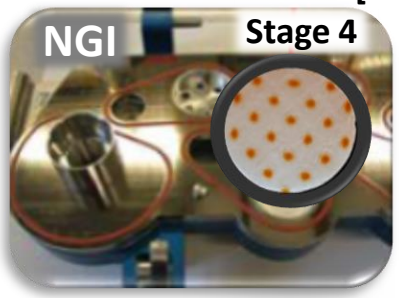
- ***Different dissolution methods were shown to have value.***
  - ***Which method to use, and is more than one method or variation on method conditions warranted?***
  - ***Can methods be too discriminatory/sensitive, hence, not biorelevant?***

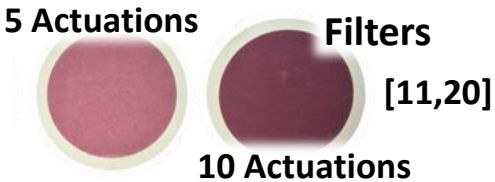
Dissolution of OIDPs: Key Features

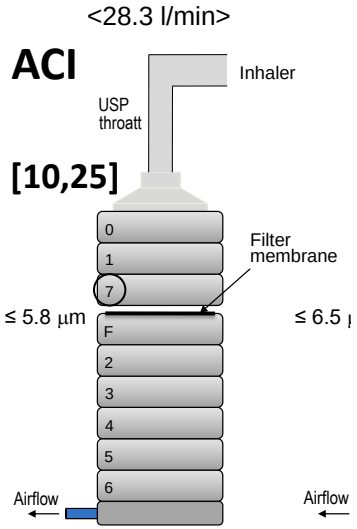
- Sample Collection
- Dissolution Apparatus
- Dissolution Media
- Method Validation
- BE assessment

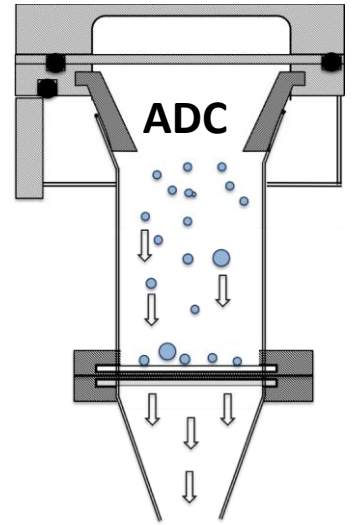
Sample Collection

- Collection of ***aerosolized fraction*** is expected.
  - DUSA
  - Ex-throat fraction (using MT model and filter)
  - Cascade impactors (NGI, FSA, ACI)
  - ADC system
- ***Dosing effect*** can occur; ensure control of # actuations.









Ongoing Questions

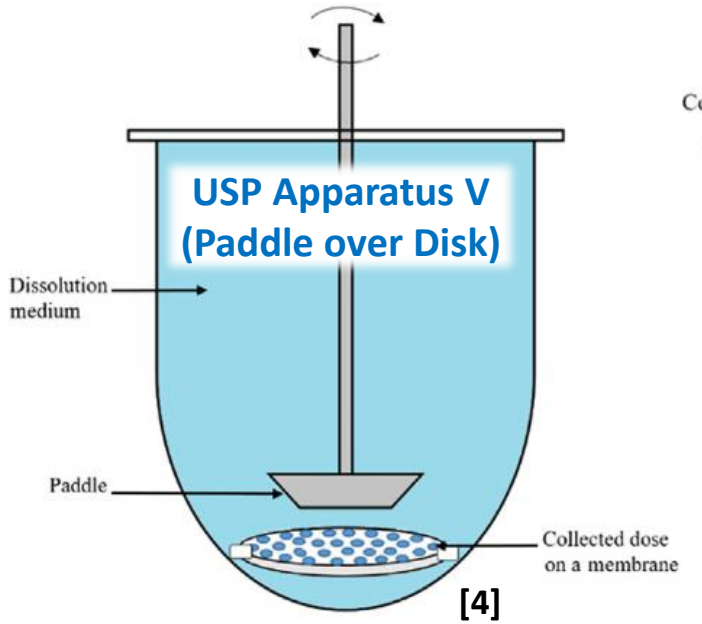
- ***Which fraction is most relevant to collect?***
  - ***Fraction existing the device (DUSA), total aerosolized fraction that can (ex-throat fraction or ADC, fast-screening impactors), specific aerosolized fractions on CI stages (ACI/NGI), or more than one?***
  - ***Choice may depend on purpose/goal of the dissolution measurement (e.g., formulation differences, establishing links to PK, for input into in silico models).***

Dissolution Apparatus

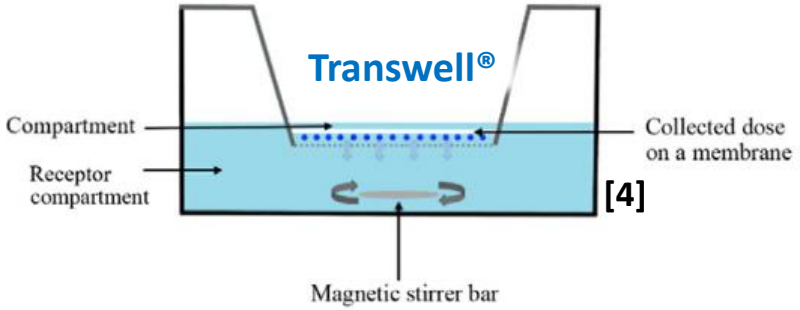
- ***Choice of dissolution apparatus should be fit for purpose.***

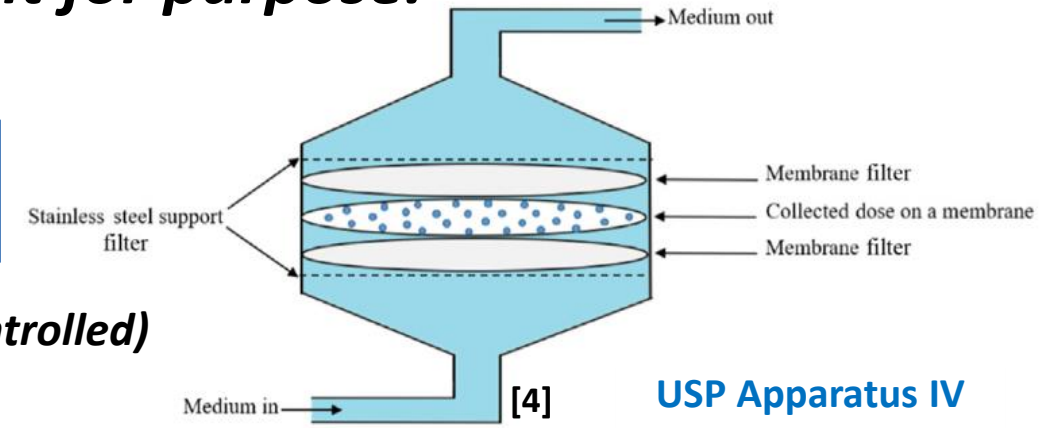
Formulation Factors → **Dissolution** → **IVIVCs**

Sink Conditions



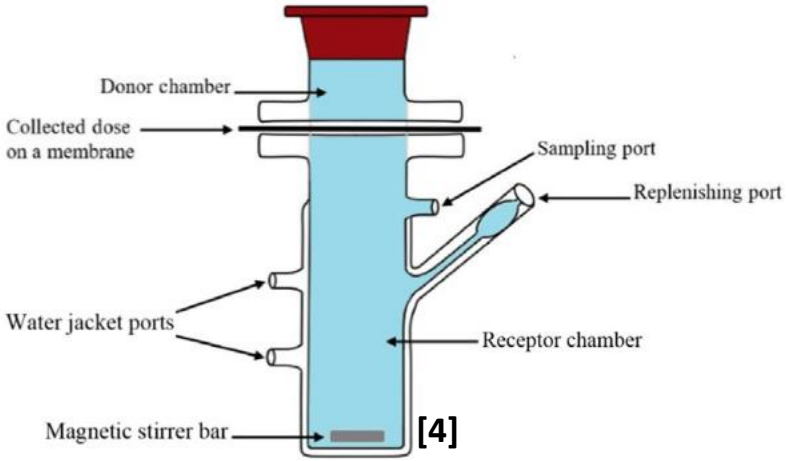
Non-Sink Conditions (Diffusion Controlled)





USP Apparatus IV (Flow-Through Cell)

Flow Through Systems



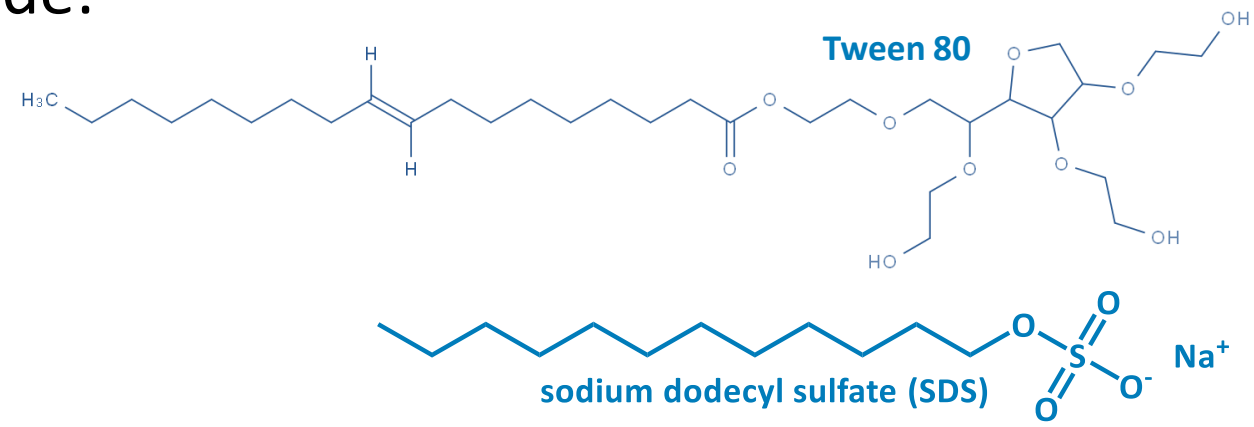
Franz® Diffusion Cell

Ongoing Questions

- ***Sink vs. non-sink vs. flow through?***
- ***Comparable dissolution behavior?***
- ***Comparable sensitivity and discriminatory ability?***
- ***Most biorelevant?***

Dissolution Media

- The choice of dissolution media should be optimized to be ***discriminatory*** and/or ***biorelevant***, which can include:
  - **Buffer**
  - **Surfactants (e.g., Tween, SDS)**
  - **Simulated Lung Fluid (SLF)**



Ongoing Questions

- ***Optimization is product dependent. Can a balance be reached between most discriminatory and most biorelevant?***
  - ***Use of buffers and/or surfactants allow for optimization in discriminatory ability of the method, but are they the most physiologically relevant?***
  - ***SLF may be most physiologically-relevant but may be optimal for discriminatory purposes to evaluate BE?***

Method Validation

- Expect the dissolution method to be properly validated and robust
  - **Predictability**
    - Correlation between ***formulation factors***, ***dissolution***, and ***in vivo performance***
  - **Discriminatory Capability/Sensitivity**
    - Compare dissolution profiles of:[26]
      - Formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variable (e.g., by 10-20%).
      - Stressed samples.
    - The ultimate **goal** is the understand the release mechanisms and determine whether the dissolution procedure can show **change** in **critical quality attributes** of a drug product

Ongoing Questions

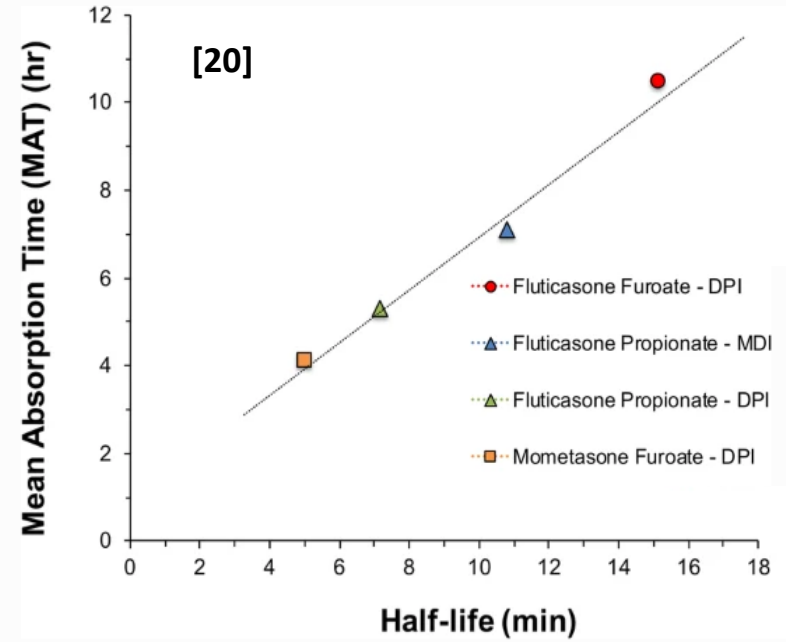
- ***What are best practices to demonstrate the robustness and discriminatory capability of the dissolution method for inhalation products?***
  - ***Ranging API particle size?***
  - ***Changes in formulation (excipient ratios)?***
  - ***Stress Conditions?***

BE Assessment

- **Model the entire dissolution profile**
- **Choose the appropriate statistical analysis for BE**
  - Model independent (e.g., ***similarity factor, f2***)
  - Model dependent
- **Establish IVIVCs**
  - ***Mean Dissolution Time (MDT)*** can be used to correlate in vitro dissolution rated to in vivo absorption rate.[4,27]
  - ***Dissolution half-life ($t_{0.5}$)*** to can be correlated to PK ***mean absorption time (MAT).***[11,20]

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\}$$

$$MDT = \frac{\sum_{j=1}^{n} \Delta M_j * t_j}{\sum_{j=1}^{n} \Delta M_j}$$



Ongoing Questions

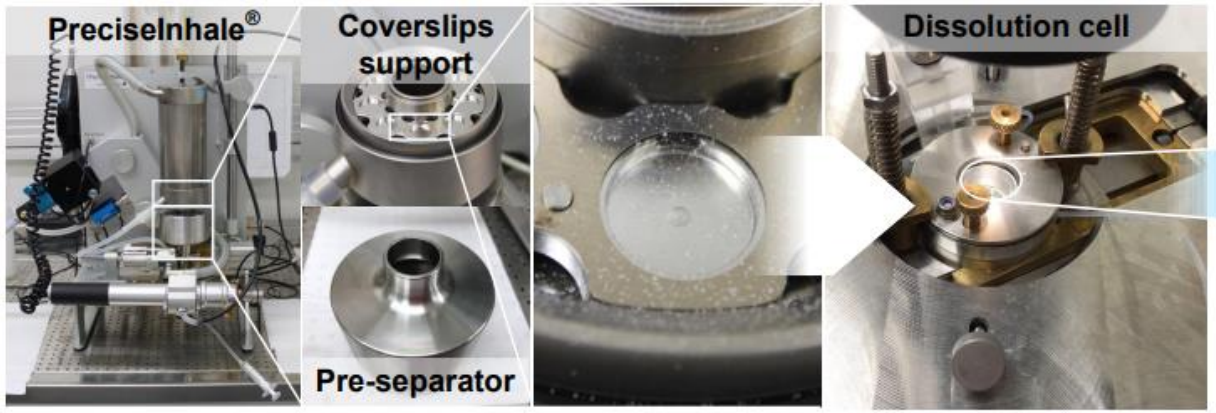
- ***What are the key parameters be used to evaluate dissolution for BE assessment or establishing IVIVCs?***

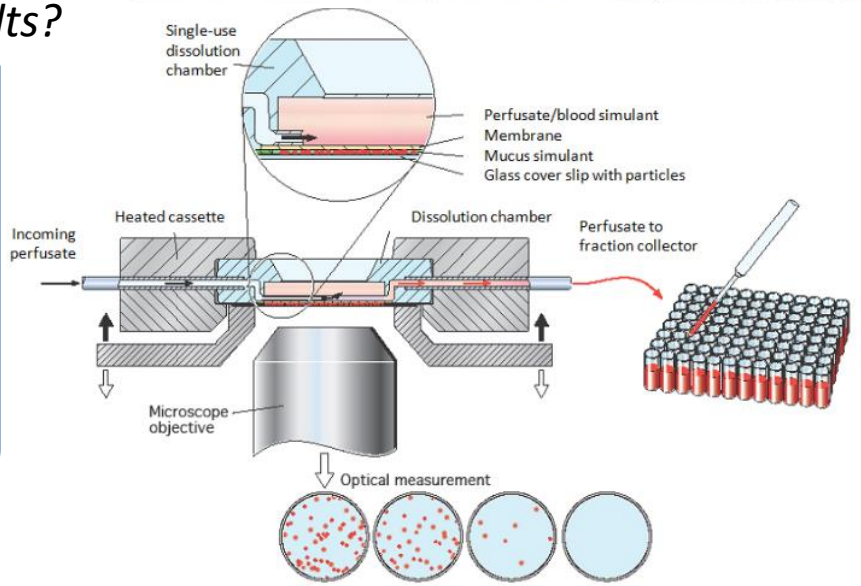
Specialized Dissolution Methods

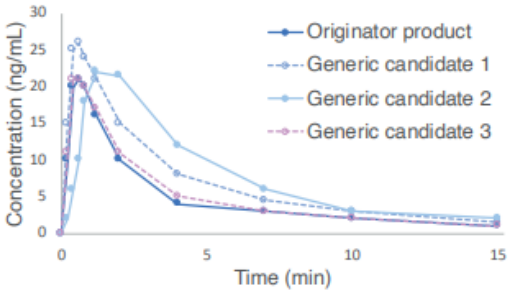
The Agency has ongoing efforts for establishing robust dissolution methods as part alternative BE approaches for inhalation products.

- **DissolvIt System:** *a dissolution model which simulates the physiological conditions in the lung and mimics the pharmacokinetic data of inhaled particles.*[28,29,30]
  - *Potential to establish IVIVCs?*
  - *Sensitive/discriminatory to formulation differences?*
  - *Can validate connection to in vivo PK results?*

- ***The Agency is open to develop novel dissolution methods.***
  - *Pre-ANDA product development meeting process*
  - *Public workshops/meetings, research projects, and conferences*







Thoughts to Consider

Lessons Learned

- Dissolution provides a ***link between product performance (formulation, device) and regional bioavailability*** and ***help establish potential IVIVCs to systemic PK performance.***
- ***More than one method*** has been shown to be ***discriminatory*** and ***sensitive.***

Ongoing Questions

Dissolution Method:

- ***Should entire aerosolized dose or more specific aerosolized fractions or both be the focus for assessment?***
- ***Sink vs. non-sink vs. flow through conditions?***
- ***What are best practices to demonstrate a robust and discriminatory dissolution method?***
- ***Additional parameters be considered for BE assessment or establishing IVIVCs?***

Thoughts to Consider cont.

Ongoing Questions

Role of Dissolution for Bioequivalence Assessment of MDIs and DPIs:

- ***Is dissolution necessary to evaluate for every MDI and DPI drug product?***
  - *Dependent on formulation and API physiochemical properties.*
  - *Dissolution limited vs. diffusion-limited (permeability).*
- ***Should dissolution serve more as a primary standalone BE/quality control tool (pivotal evidence), as a supportive role to establish IVIVCs and in silico methods, or both?***
  - *Which method(s) you choose may depend on purpose of dissolution serves as part of the alternative BE approach.*
- ***Other supportive physiologically-relevant methods, e.g., in vitro and ex vivo respiratory models, more suitable for consider when attempting to establish IVIVCs or inputs to in silico models?***
  - *Be able to capture other physiological parameters not considered in dissolution but relevant to lung absorption.*

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  - Manoush Masarrat


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12. Contract 75F40122C00197, *Dissolvit® – An In Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating The Dissolution and Absorption of Drugs Administered Via the Inhalation Route,* Manoush Masarrat and Maria Malmlöf, Inhalation Sciences Sweden AB **(Ongoing)**

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13. Grant 5U01FD004943, *Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance,* Guenther Hochhaus, University of Florida **(Complete)**
14. Contract HHSF223201610099C, *Pharmacokinetic Comparison of Locally Acting Orally Inhaled Drug Products,* Jurgen B. Bulitta, University of Florida **(Complete)**
15. Contract HHSF223201710116C, *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches,* Robert Price and Jag Shur, University of Bath, **(Complete)**
16. Contract HHSF223201810169C, *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers,* Hugh D.C. Smyth, University of Texas at Austin **(Ongoing)**
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