The Current Status and Considerations for Dissolution Testing of Orally Inhaled Drug Products (OIDPs)

Society for Pharmaceutical Dissolution Science US Chapter Webinar

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- *This presentation reflects the views of the author and should not be construed to represent FDA's views or policies, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

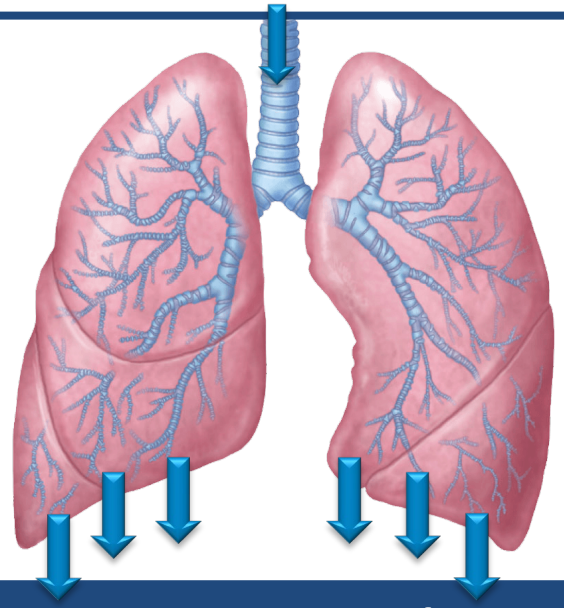
Outline

- Provide an overview to how ***dissolution*** is beneficial to understanding ***inhalation drug products***
  - **Drug Delivery to the Lungs**
  - **Role of Dissolution**
  - **Dissolution Methodology**
  - **Dissolution Capabilities**
  - **Future of Dissolution – Challenges and Opportunities**

Why Drug Delivery to the Lungs?

Local Lung Delivery

- *High local availability*
- *Low systemic exposure*



Systemic Lung Delivery

- *Noninvasive*
- *Rapid Pharmacokinetics*
- *Circumvent Hepatic Clearance*

Local Diseases

- *Asthma*
- *COPD*
- *Cystic Fibrosis*
- *Infections*
- *Pulmonary arterial hypertension (PAH)*
- *Respiratory Distress Syndrome (RDS)*
- *Cancer*

Systemic Diseases

- *Diabetes*
- *Schizophrenia*
- *Parkinson's disease*
- *Smoking*
- *Acute Agitation*

Therapeutics

- *Bronchodilators*
- *Glucocorticoids*
- *Chromones*
- *Anti-infectives*
- *Mannitol*
- *Surfactants*
- *Pulmonary Vasodilators*
- *Peptides + Proteins*
- *RNA*

Delivery Platform

- *Nebulizers*
- *Metered Dose Inhalers*
- *Dry Powder Inhalers*
- *Soft Mist Inhalers*

 Reference: [1]

Inhalation Drug Product Marketplace

- Global market for inhalation drug delivery is expected to ***rise***
  - **Increased prevalence** of ***asthma***, ***cystic fibrosis***, and ***COPD*** worldwide (The Global Asthma Report 2022)[2]

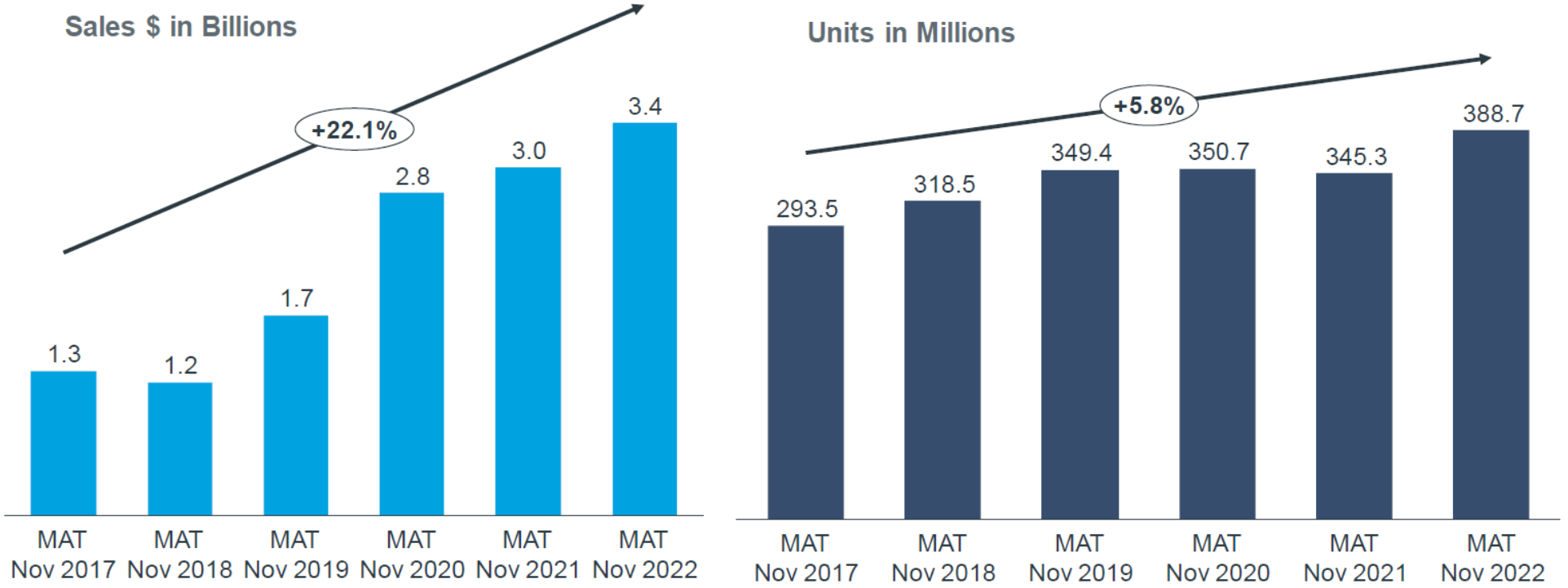
Inhalation Drug Product Market[3]

Inhaled Drug Products	2017 Market Share	MAT June 2022 Share
Brand	3.8%	3.8%
Generic	**2.1%**	**6.0%**
Total (Brand + Generic)	3.9%	3.9%

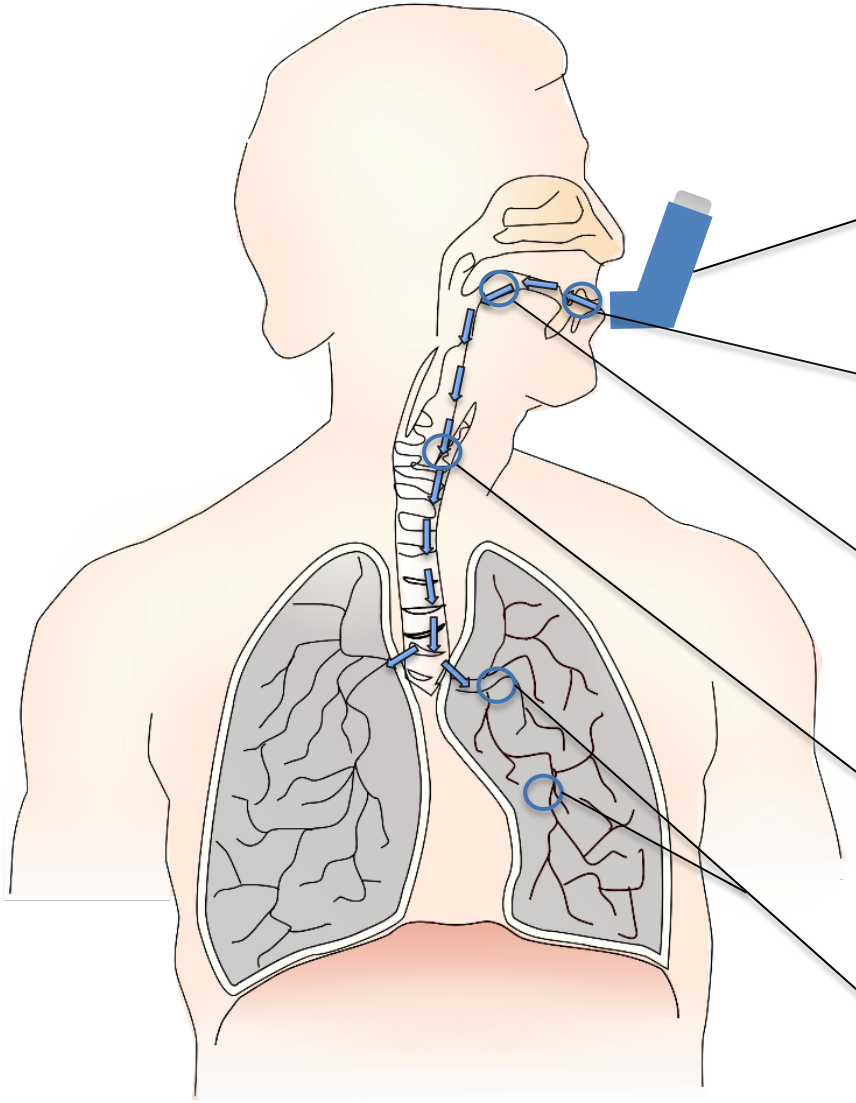
Inhalation Drug Product Marketplace: Generics

- **Generics**: ***Cost savings + Market Growth!***
  - High costs → non-adherence → lack of optimal care
  - Improved access to inhalers→ improvement in medication adherence → decrease in the overall economic burden of asthma and COPD in the USA [4]

Unbranded Generic Inhalants CAGR Sales and Units[3]



Contributing Factors for Local Drug Delivery



Step 1
Formulation/Device Characteristics

Step 2
Actuation and Aerosolization

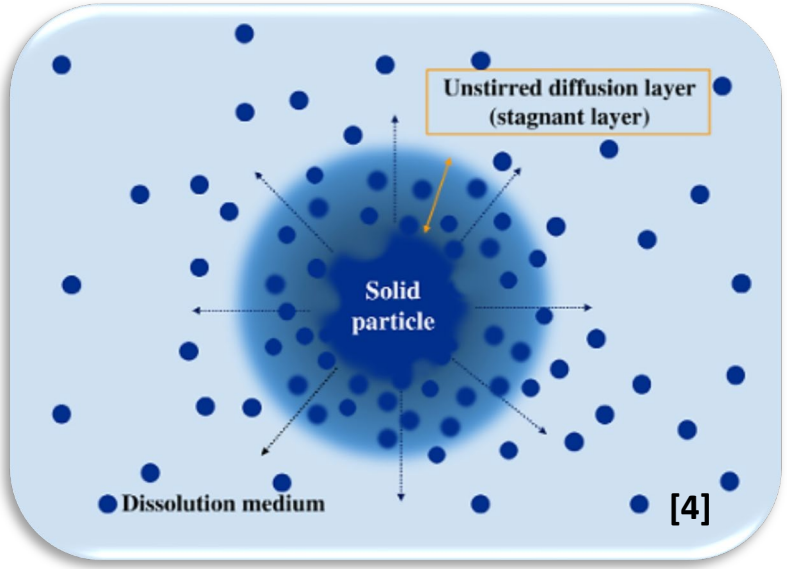
Step 3
Formulation Post-Actuation

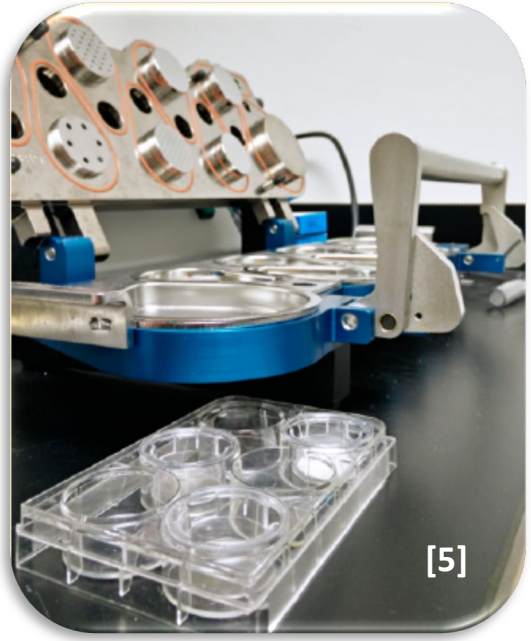
Step 4
Airway Transit

Step 5
Deposition, Dissolution, Absorption

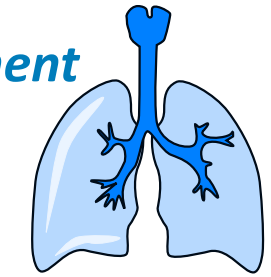
The Role of Dissolution

- **Dissolution:**[5,6] 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

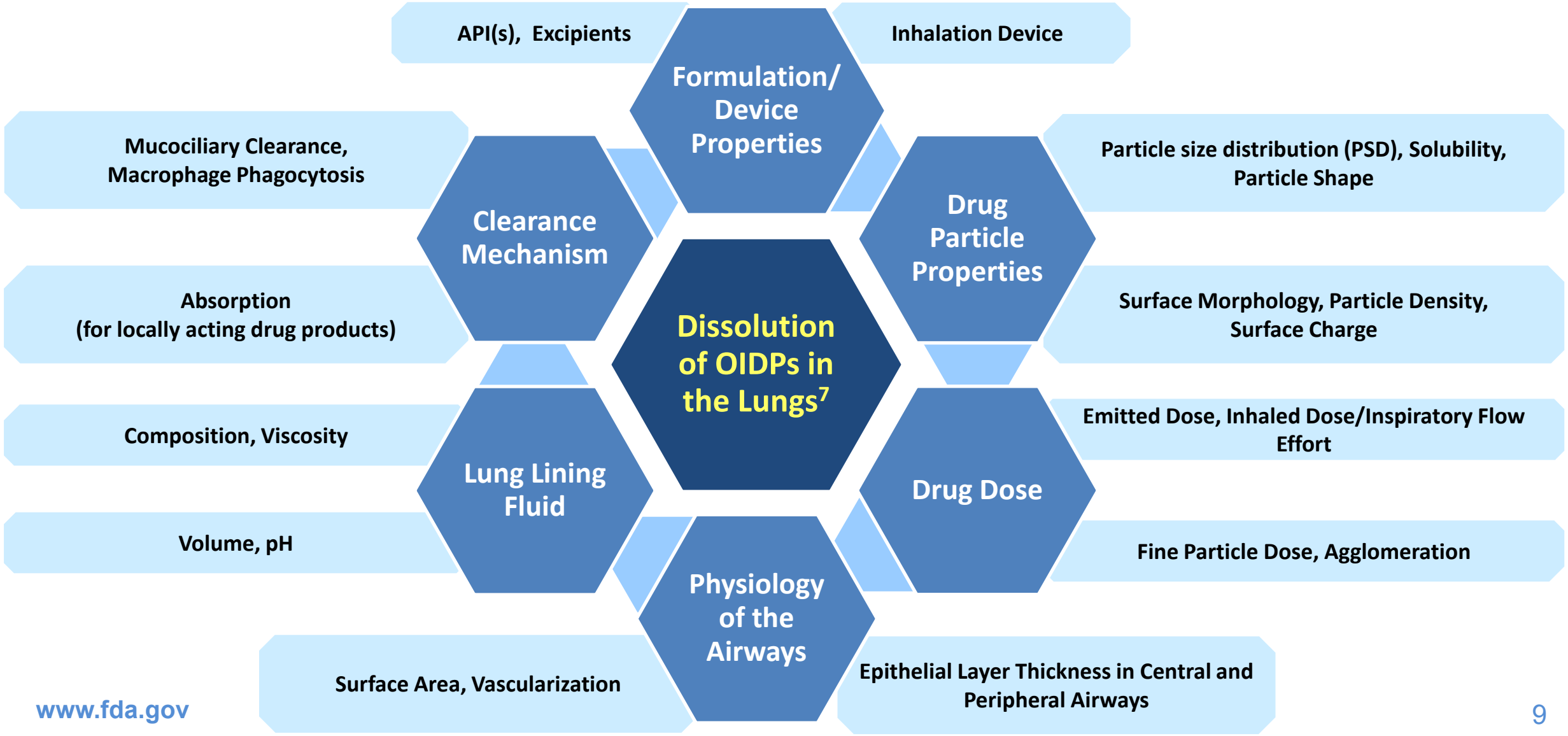




- In the context of inhalation drug products, dissolution may be useful for:[6]
  - ***A product quality control tool***
  - ***Bioequivalence (BE) assessment for generic drug development***
  - ***Establishing in vitro-in vivo correlations (IVIVCs)***
  - ***Input into in silico models***



Factors Relevant to Dissolution of OIDPs



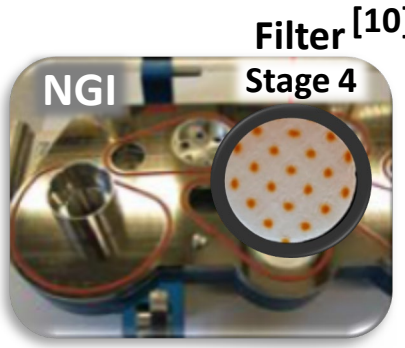
Dissolution of OIDPs: Key Features

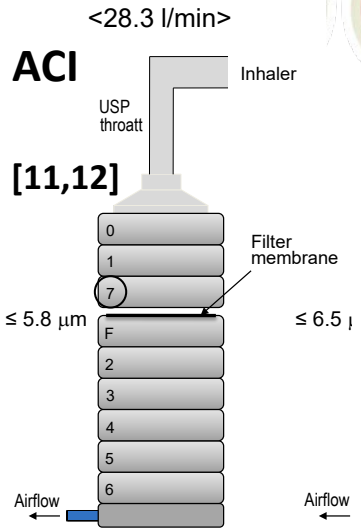
- Sample Collection
- Dissolution Apparatus
- Dissolution Media
- Method Validation
- Assessment

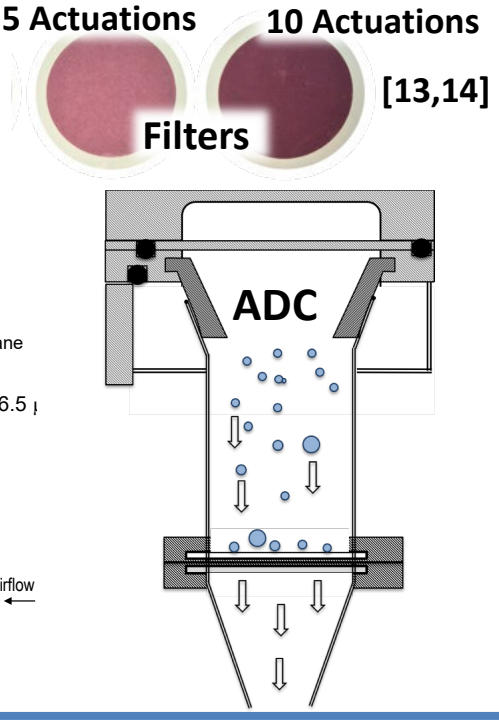
Sample Collection

Key Points

- Collection of ***aerosolized fraction*** is expected
  - Choice may depend on ***purpose/goal*** of the dissolution measurement (e.g., formulation differences, establishing links to PK, for input into in silico models)







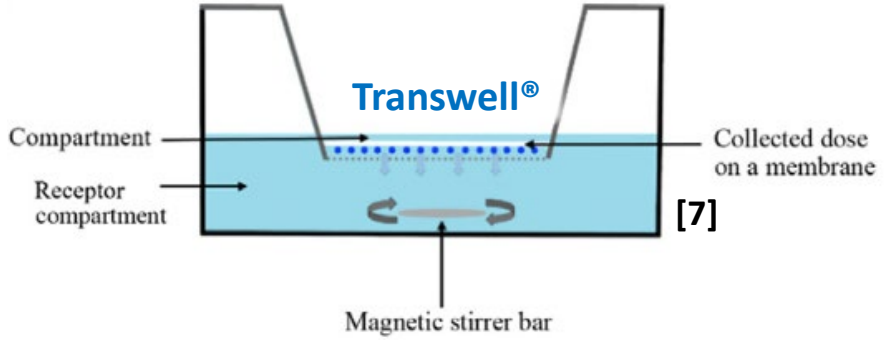
- ***Dosing effect*** can occur
  - Ensure control of ***number of actuations***

Dissolution Apparatus

Key Points

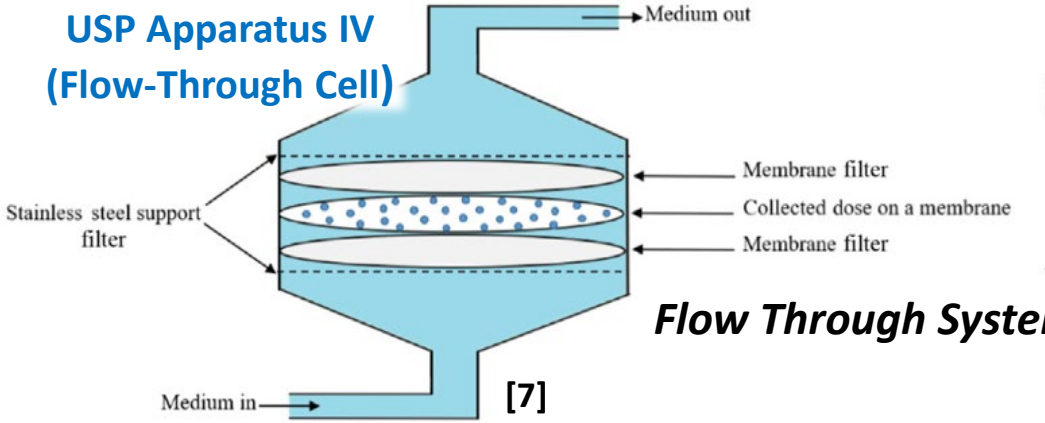
- Choice of dissolution apparatus should be ***fit for purpose***
  - Non-sink vs. sink vs. flow-through
  - Sensitivity/discriminatory capabilities

Non-Sink Conditions (Diffusion Controlled)



[7]

USP Apparatus IV (Flow-Through Cell)



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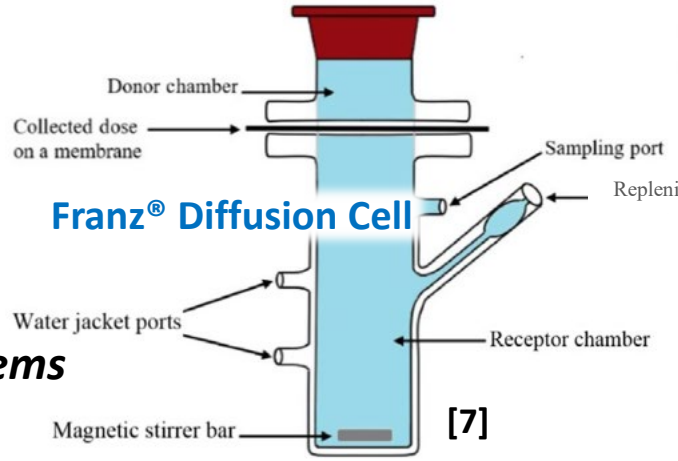
Flow Through Systems

Franz® Diffusion Cell



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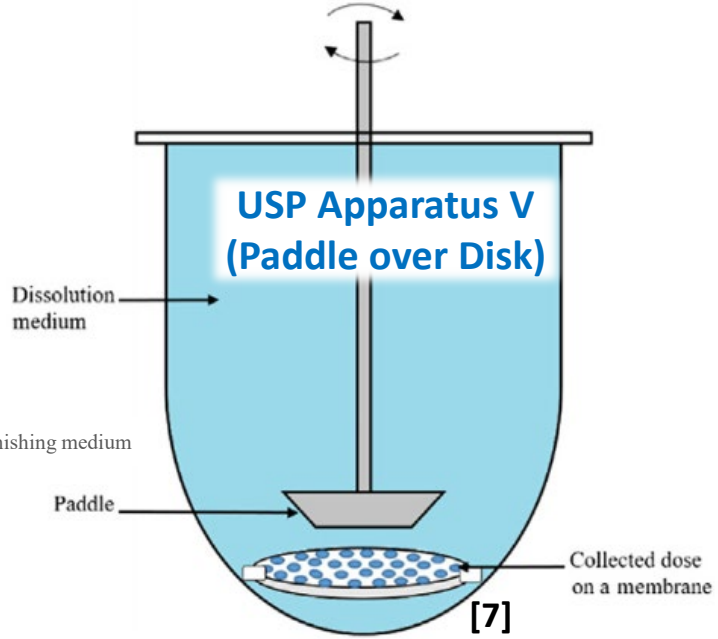
USP Apparatus V (Paddle over Disk)



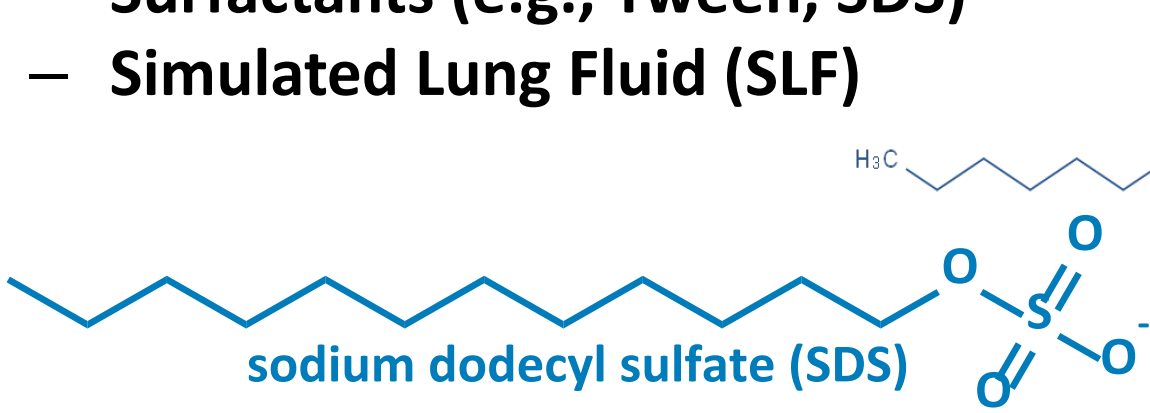
[7]

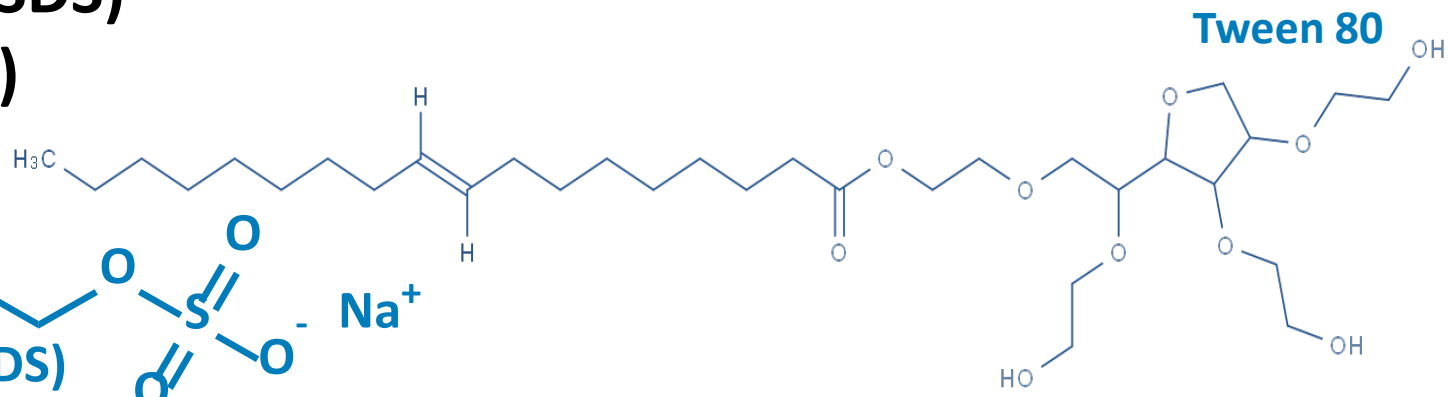
Sink Conditions

Dissolution Media

Key Points

- 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)**





- Optimization is ***product dependent***

Method Validation

Key Points

- The dissolution method should be ***properly validated*** and ***robust***
  - **Predictability**
    - Correlation between ***formulation factors***, ***dissolution***, and ***in vivo performance***
  - **Discriminatory Capability/Sensitivity**
    - Compare dissolution profiles of…[15]
      - Formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variable (e.g., by 10-20%)
        - » API particle size and/or physiochemical properties, excipient ratios
      - 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

Assessment

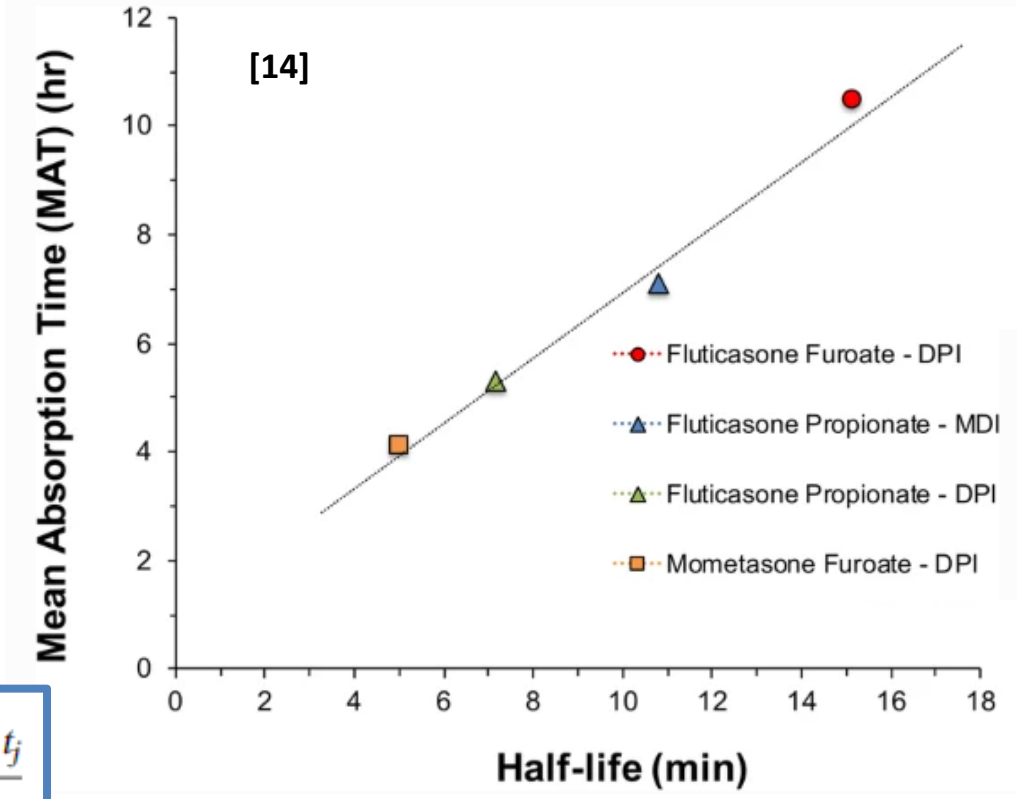
Key Points

- Model the ***entire*** dissolution profile
- Choose the ***appropriate statistical analysis*** for comparison of dissolution profiles
  - Model independent (e.g., ***similarity factor, f2***)[16]

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

  - Model dependent (linear, quadratic, logistic, probit, Weibull)
- **Establish IVIVCs**
  - ***Mean Dissolution Time (MDT)*** can be used to correlate in vitro dissolution rated to in vivo absorption rate[7,17]

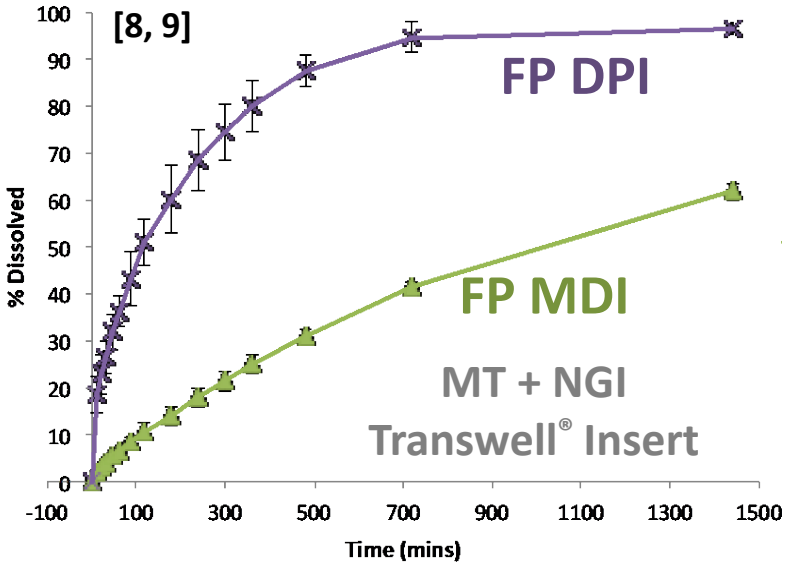
$$MDT = \frac{\sum_{j=1}^{n} \Delta M_j * t_j}{\sum_{j=1}^{n} \Delta M_j}$$

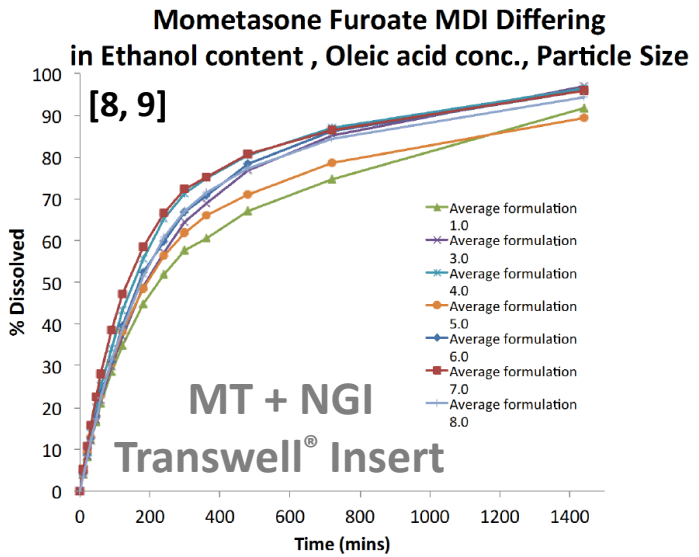


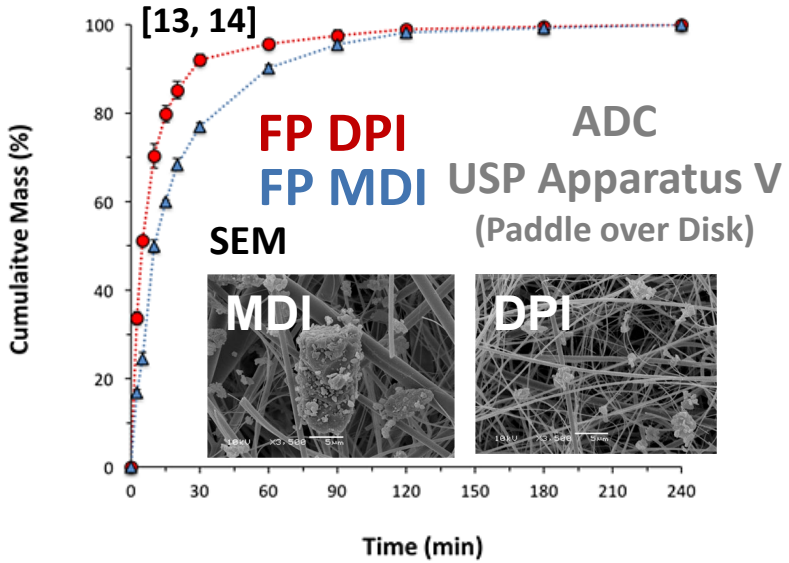
Dissolution and Formulation Differences

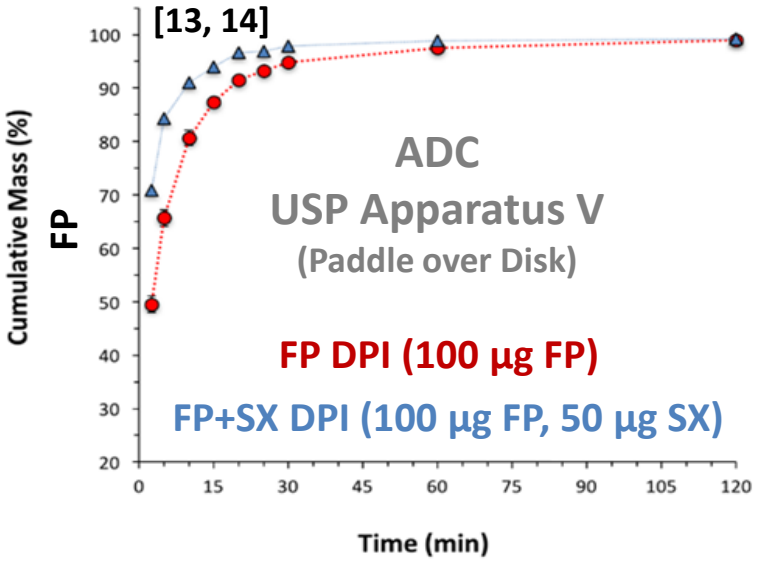
- **In vitro dissolution is able to capture *differences in formulations*:[8,9,13,14]**
  - **MDI vs. DPI**
  - **API particle size and excipient differences**
  - **Absence/presence of API**

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



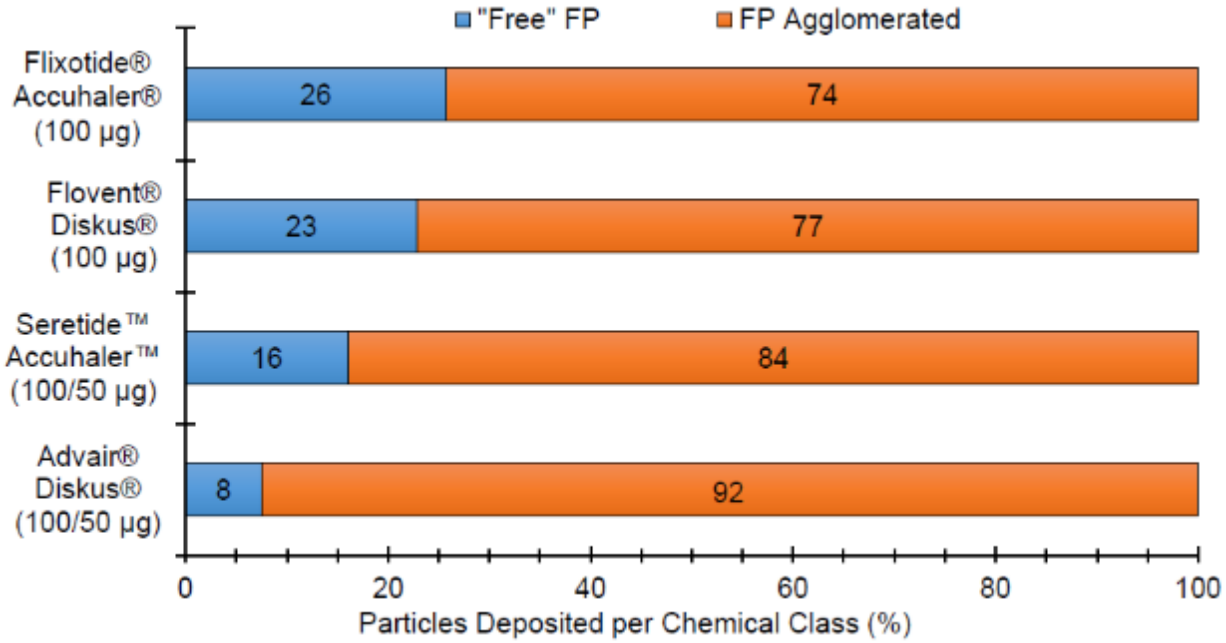


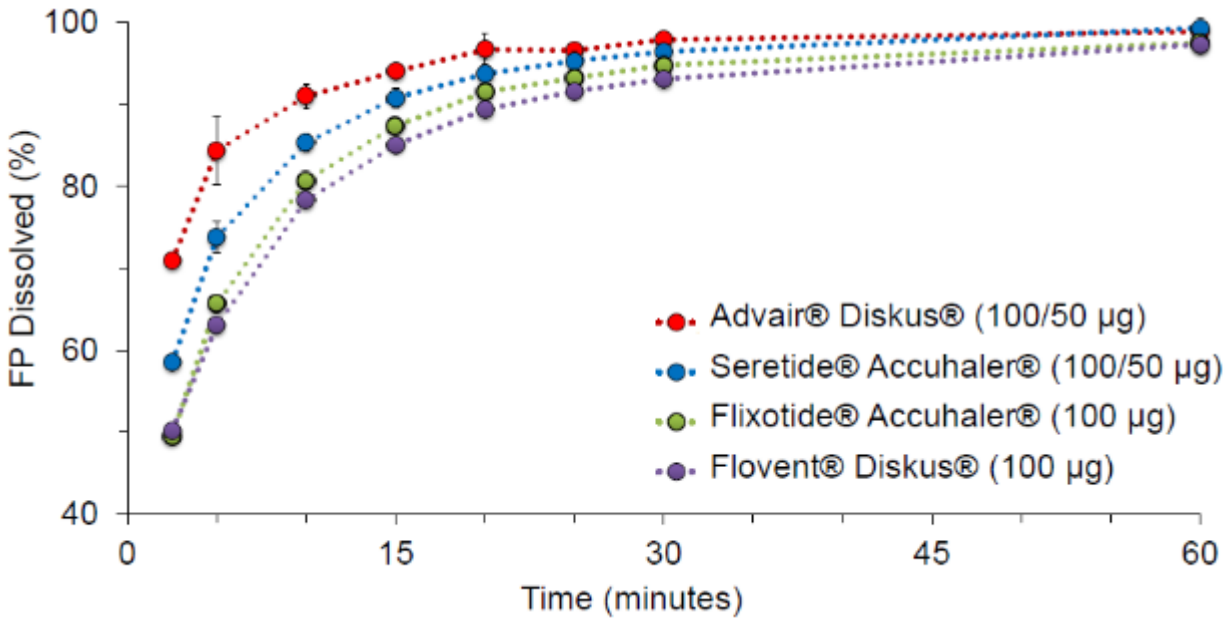




Microstructure and Dissolution

- **In vitro dissolution is able to capture differences in *microstructure*[15,21]**





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

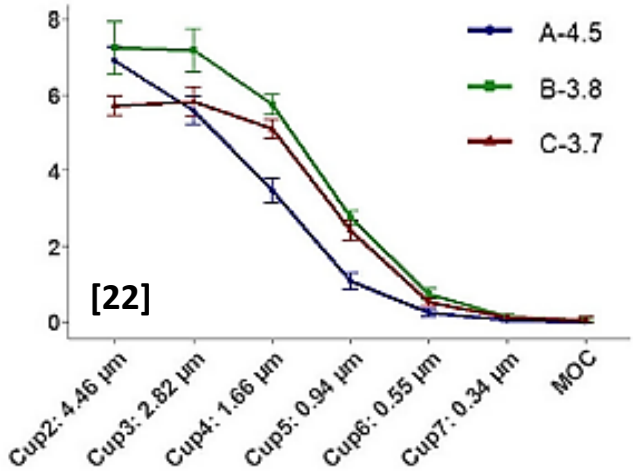
In vitro dissolution modified USP Apparatus V of ISM dose collected from equivalent 500 mcg FP

Differences in API, Fluticasone Propionate (FP), agglomerated to the excipient lactose demonstrates difference in dissolution behavior between US and EU marketed products[18,19]

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

Dissolution and PK

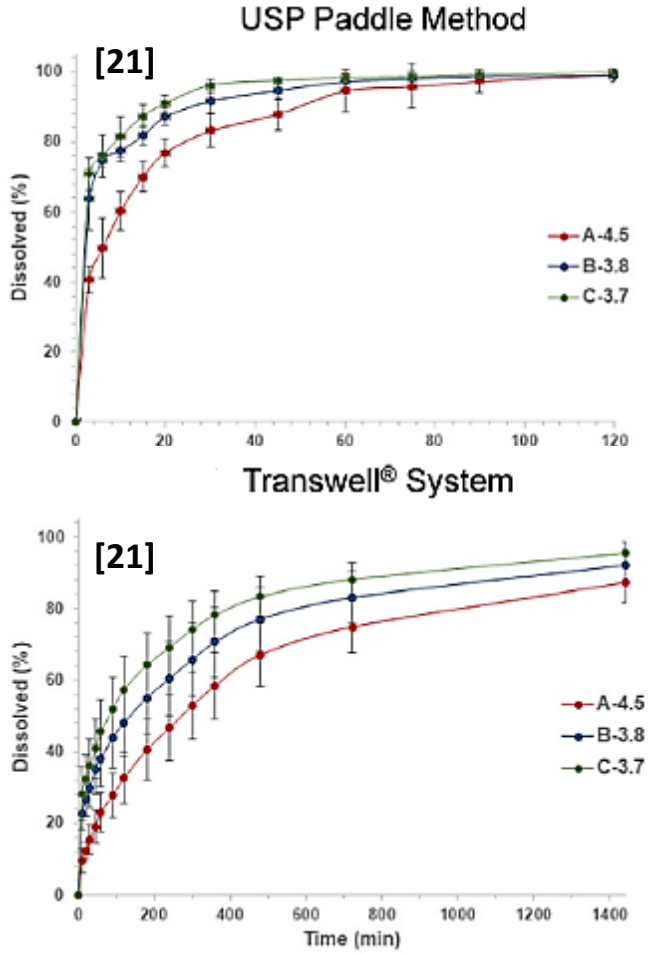
- **Potential for correlating dissolution to *systemic PK*** [8,20,21,22]
  - Fluticasone propionate (FP) DPI Formulations
    - Same API batch (and particle size)
    - Different lactose fines
    - *Different aerosol performance*:
      - A: 4.5 µm MMAD
      - B: 3.8 µm MMAD
      - C: 3.7 µm MMAD



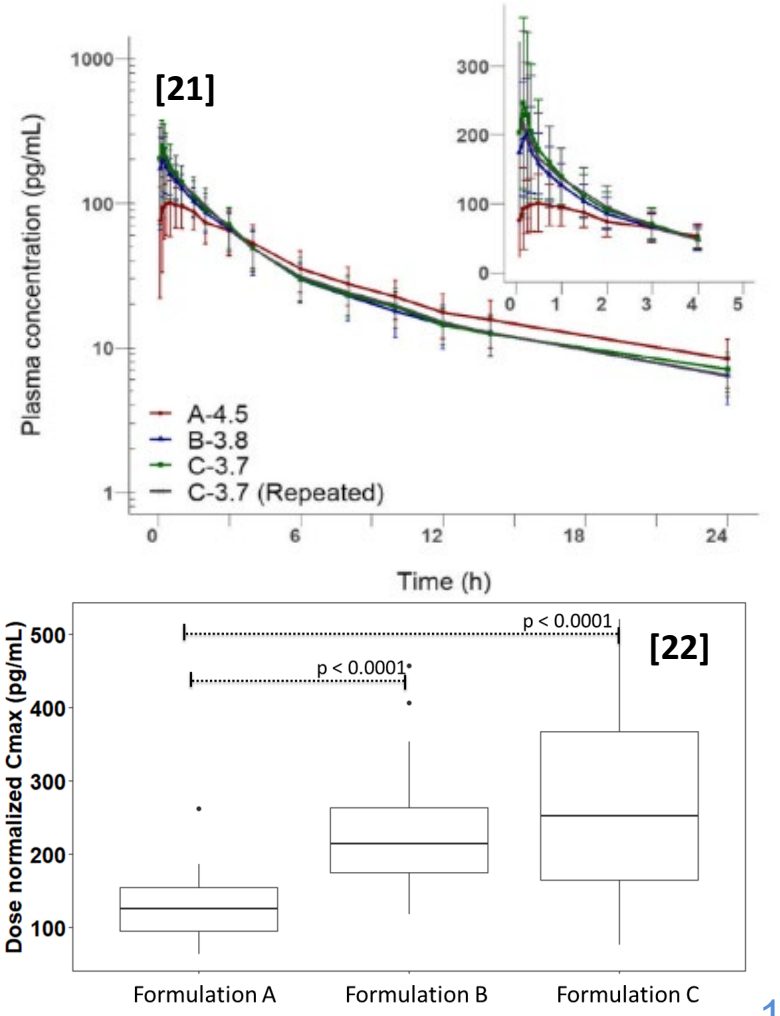
MMAD: median mass aerodynamic diameter

$TLD_{in\ vitro}$: amount of drug mass passing through a mouth-throat model

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

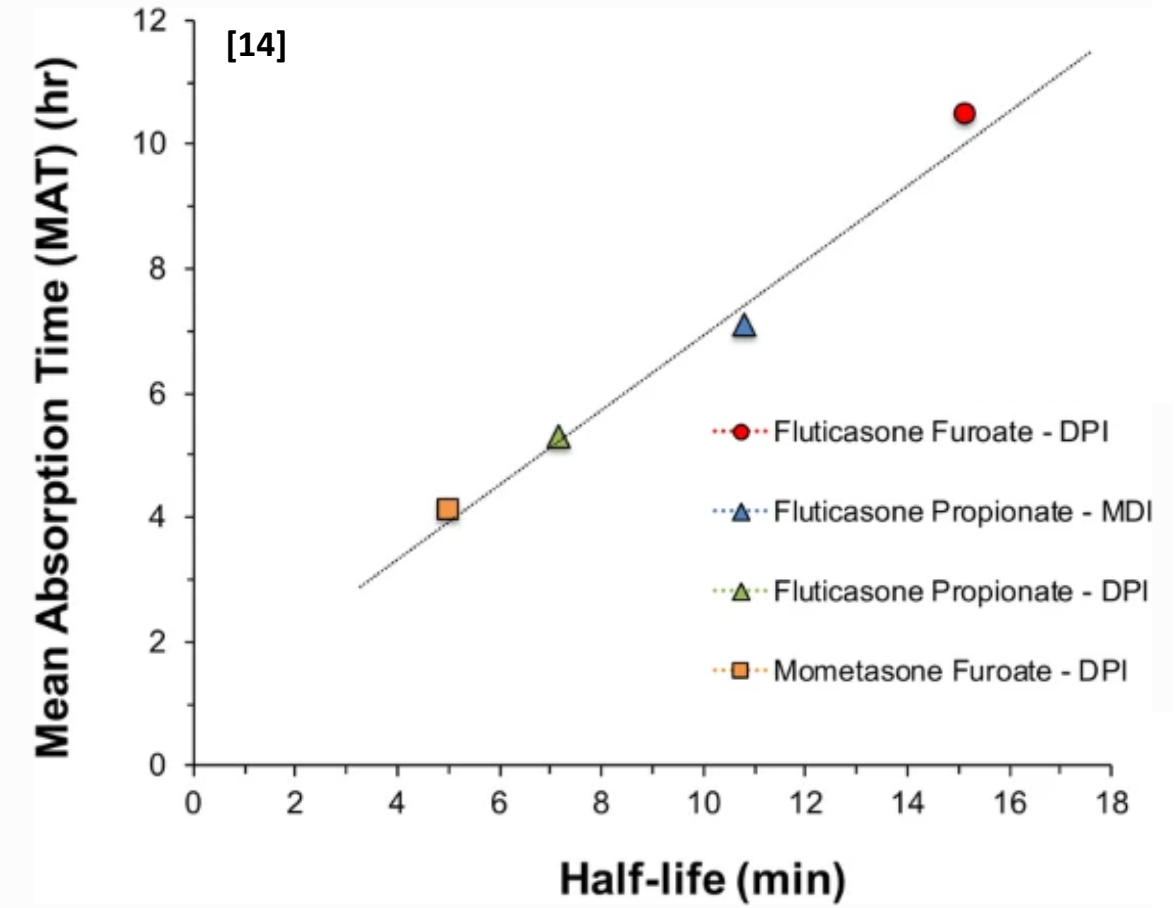


- *Differences in PK parameters* (C_{max})



Dissolution and PK

- **Potential for correlating dissolution to *systemic PK***
  - Link ***mean absorption time (MAT)*** from PK measurements and ***dissolution half-life ($t_{0.5}$)*** for inhaled corticosteroids[13,14]



Dissolution Capabilities

- **<u>Lessons Learned</u>:**
  - 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

The Future: Challenges and Opportunities

Challenge: No standardized methods of dissolution for inhalation products

- **Opportunities:**
  - Multiple methods are capable of being sensitive, and discriminatory. Choose most suitable method to meet one's needs
  - Room for development of new methods

Challenge: When is dissolution necessary – should it be used to evaluate every MDI and DPI?

- **Opportunities:**
  - Understand your drug product: dissolution limited vs. diffusion-limited (permeability)
  - Potential to develop a bioclassification system for inhalation products (iBCS)

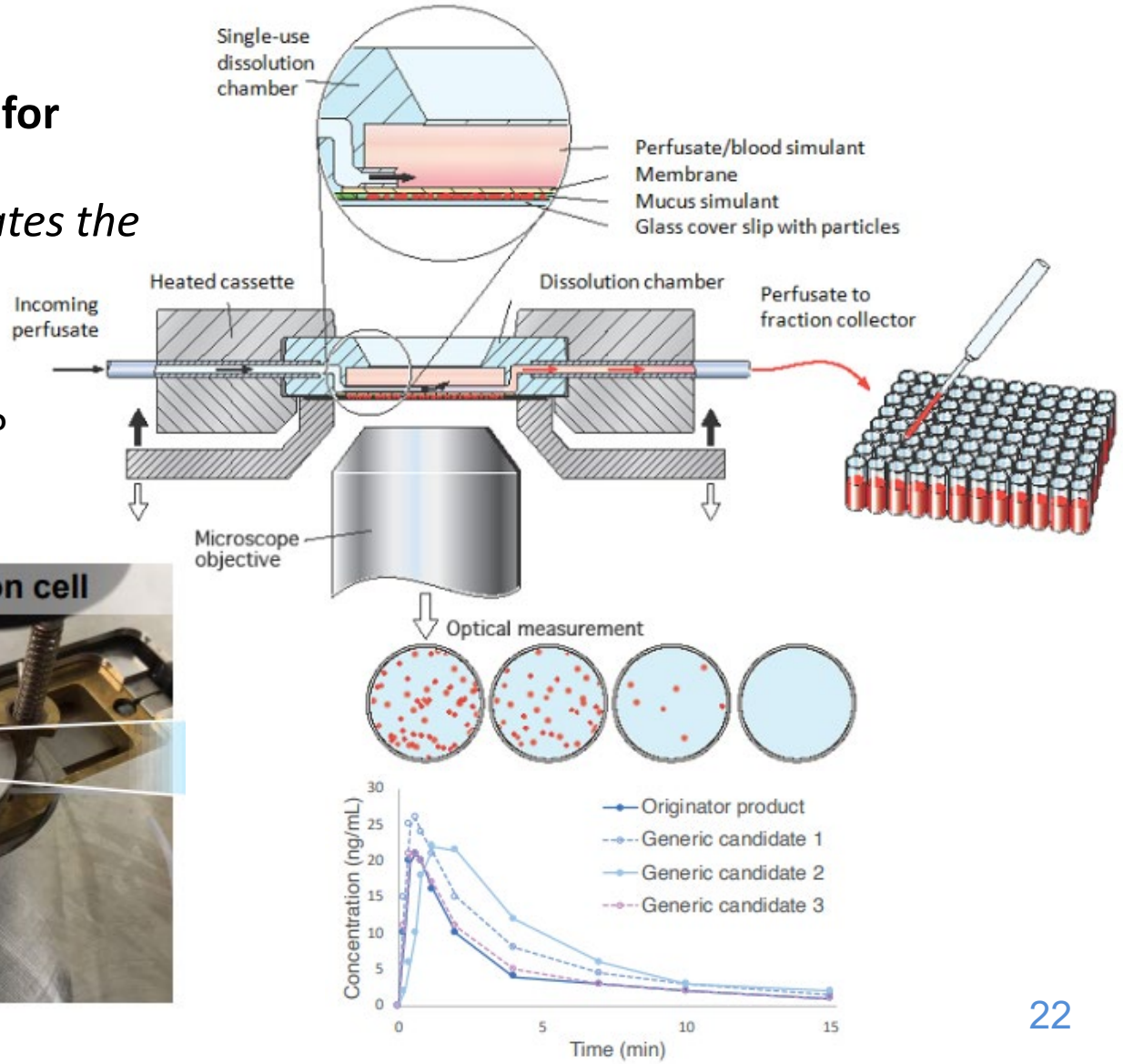
Challenge: Dissolution may not be representative of in vivo situation

- **Opportunities:**
  - Understand benefits/limitations
  - Combine with other orthogonal techniques to build IVIVCs
    - In vitro, ex vivo respiratory models, in silico

Specialized Dissolution Methods

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

- **DissolvIt® System:** *a dissolution model which simulates the physiological conditions in the lung and mimics the pharmacokinetic data of inhaled particles.*[23,24,25]
  - Potential to establish IVIVCs?
  - Sensitive/discriminatory to formulation differences?
  - Can validate connection to in vivo PK results?



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