Dissolution testing for orally inhaled products: science, practice, regulation

Ben Forbes
Not a new topic

• interaction of a droplet on deposition?
• rate of particle dissolution?
• influence of lung lining fluid?
• nature of pores in different regions of the lung?
• effect of disease?
• type and distribution of transporters?
• effect of inhaled medicines on lung permeability?

Not a new topic

• rate of particle dissolution?
• influence of lung lining fluid?
• effect of disease?
Different roles for dissolution testing

1. *In vitro* dissolution as a critical product characteristic, e.g. as a test show whether the aerosol particles emitted from batch/product A are equivalent to those from batch/product B

2. *In vitro* dissolution (& absorptive profiling) as a means of probing *in vivo* inhalation biopharmaceutics, i.e. mechanistic understanding to guide formulation development
   e.g. engineered particles, excipient selection and new materials

Different methods for dissolution testing

- Aerosol collection
- Exposure to dissolution medium
- Measurement of drug release
- Interpretation of data

<table>
<thead>
<tr>
<th>Next Generation Impactor (MMAD)</th>
<th>Dissolution Assay (F2)</th>
<th>Pharmacokinetics (AUC)</th>
<th>Interpretation</th>
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<td>T = R</td>
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<td>1. Bioequivalent</td>
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<td>T ≠ R</td>
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<td>2. <em>In vivo</em> differences due to volunteer-product interface</td>
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<td>3. Pharmaceutical difference suggested by dissolution assay has no impact <em>in vivo</em></td>
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<td>4. Suggestion of formulation-driven pharmacokinetics</td>
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<td>5. Despite different <em>in vitro</em> deposition, formulations are equivalent <em>in vivo</em></td>
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<td>6. Impact of regional deposition determines non-equivalence</td>
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<td>7. Despite differences in <em>in vitro</em> tests, the net effect is equivalence</td>
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<td>T ≠ R</td>
<td>8. Non-bioequivalent</td>
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Dissolution testing
The fall and rise of dissolution testing for inhaled products
(2012 - present)
“...could not find any compelling evidence suggesting that dissolution testing is kinetically and/or clinically crucial for currently approved inhaled drug products.”
RDD 2012

- A USP perspective on dissolution testing for aerosol drugs
  AJ Hickey

- A prospective dissolution test design: controlling important variables
  YJ Son and JT McConville

- Understanding dissolution in the presence of competing cellular uptake and absorption in the airways
  M Sakagami and DA Lakhani

- QbD demands for powder inhalers of the future: addressing dissolution during product development
  AD Cooper, M Ticehurst and RN Jones

- If dissolution release testing for inhaled products is relevant, then how? An IPAC-RS perspective
  D Christopher and M Dey
Dissolution becoming mainstream ...

The lung as a dissolution vessel?

Do we understand the biorelevance of drug dissolution in the lung?

Jayne E. Hastedt
JP Pharma Consulting, LLC

Dissolution testing:
The United States Pharmacopeia (USP) Dissolution Apparatus 1 (rotating basket) was first introduced in 1976 for oral drug products. The dissolution test is a quality control tool to assess batch-to-batch variation, an aid in formulation development, and a means to link in vitro product release profiles to in vivo product performance for oral products. The current issues associated with dissolution testing for oral products are the discriminating power of the method, utilizing test conditions and media that are indicative of the in vivo environment, and establishing a link between in vitro data and in vivo product performance (in vivo). Dissolution test apparatus have evolved over the years, and application has expanded to oral integrated, non-parenteral, and other novel and nonconventional dosage forms. The Quality by Design (QbD) "desired state" for dissolution testing is to be able to predict the product bioperformance based on in vitro data.

Over the past 10 years, there has been an increased interest in developing dissolution test methods for novel dosage forms. In 2013, the International Federation of Pharmaceutical Sciences (IFP), and the American Association of Pharmaceutical Sciences (AAPS) published a position paper containing guidelines for dissolution testing of novel or special dosage forms. The authors proposed "first choice" test methods using existing apparatus for these novel/special dosage forms. A follow-up workshop sponsored by the IFP Special Interest Group (SIG) on Dissolution/Drug Release in conjunction with the Royal Pharmaceutical Society of Great Britain (RPSGB) was held in 2014 on the in vitro drug release from special dosage forms. This workshop was the first to specifically discuss the role of dissolution for inhaled and inhalation products. In 2009, another joint workshop sponsored by the AAPS and IFP SIG on Dissolution/Drug Release was held to review the latest advances in dissolution testing for novel dosage forms and resulted in an update to the 2005 publication on this topic. In this publication, the authors noted that although there is not a dissolution test method in place for inhaled and inhalation products, there might be value in understanding drug release from inhaled particles and droplets deposited in the lung. Over the same period of time, there has been increased interest in developing dissolution test apparatus and methods specifically for inhalation products. Much of the interest in dissolution testing for inhalation products came directly from various treatment areas ...
GDUFA OIDP Dissolution Grant

Three grants awarded in 2013:

- In vitro fluid capacity-limited dissolution testing and its kinetic relation to in vivo clinical pharmacokinetics for orally inhaled drug products
  Masahiro Sakagami, Ph.D.
  Virginia Commonwealth University

- Development of an in vitro dissolution technique to understand the clinical based outcomes of orally inhaled drug particles
  Robert Price, Ph.D.
  University of Bath

- An optimized dissolution test system for orally inhaled drugs: Development and validation
  Guenther Hochhaus, Ph.D.
  University of Florida
Future plans for implementation

- Data from the three grants will be generated by end of 2014
- Public discussion on the data generated and get input from experts in the field
- Develop a BCS-like classification for OIDPs
- Develop standardized predictive dissolution/permeation techniques for OIDPs
FDA Dissolution Grant Outputs

University of Virginia

University of Bath
NanoPharm announce launch of a dissolution testing for inhaled drugs using the UniDose collection system (May 2016)

University of Florida
MEETING REPORT

Scope and relevance of a pulmonary biopharmaceutical classification system
AAPS/FDA/USP Workshop March 16-17th, 2015 in Baltimore, MD

Jayne E. Hastedt¹, Per Bäckman², Andrew R. Clark³, William Doub⁴, Anthony Hickey⁵, Guenther Hochhaus⁶, Phil J. Kuehl⁷, Claus-Michael Lehr⁸, Peter Mauser⁹, Jason McConville¹⁰, Ralph Niven¹¹, Masahiro Sakagimi¹² and Jeffry G. Weers¹¹
A plethora of different methods have been developed and are being utilised in academic research, in-house industrial drug development or offered commercially.

Such is the variation in method, detail and validation reported, it is impossible to compare outcomes and make recommendations towards standardised predictive methodology.

Method evaluation

2019 – 2020

Systematic comparison of dissolution methods

Standard Inhalation Test Product (Elpen, Greece)
Dissolution assays (multiple laboratories)
- Academic
- Proprietary
- Commercial service

Data analysis (common protocol)
Data interpretation and simulation
Impact of dissolution on inhaled drug pharmacokinetics

How can simulation and mechanistic modelling help us?
In vitro dissolution: bending, drug combinations and products


Modeling approaches

A variety of mechanistic models are available
- AstraZeneca - LungSim
- Merck Proprietary model
- Gastroplus (SimulationsPlus)
- Mimetikos Preludium

in vitro experiment / in silico modeling hybrid approaches
Dissolution inputs based on:
- Calculation
  (based on VMD, solubility, porosity, etc)
- Measurement
  (utilising in vitro dissolution methods)
In vitro dissolution: API and formulation effects

Dissolution rate differentiation due to different substance type and particle size

Fraction dissolved vs. Time (min)

- Budesonide
- Fluticasone Propionate
- Fluticasone Furoate
- AZD5423 (1.3 μm)
- AZD5423 (3.1 μm)

**t63 (min)** vs. **MAT (h)**

Franek et al. Mol Pharm 113: 5319-5326 (2018)
A computational model

The Model: A System of Differential Equations

- **Mathematical description** (generalized and simplified examples):
  - **Deposition Probability**: \( \eta_g = 1 - (1-\eta_g^i)(1-\eta_g^s)(1-\eta_g^d) \)
  - **Non-Absorptive Clearance**: \( \frac{dn_{ET}}{dt} \propto k_{MCC} \times n_{BB} \)
  - **Dissolution**: \( \frac{dn_{sol}}{dt} \propto \frac{D}{h} \times A_s \times (C_s-C_{ALF}) \)
  - **Permeation into Tissue**: \( \frac{dn_{tis}}{dt} \propto P_{eff} \times A_{epi} \times (C_{ALF}-C_{epi}) \)
  - **Perfusion into System**: \( \frac{dn_{sys}}{dt} \propto Q \times V_{tis} \times R_{bp}/F_{up} \times [C_{tis} - C_{sys}] \)

- *Systemic disposition is described by a non-mechanistic compartmental PK model based on IV PK data*

- **Critical Product Attributes**: Deposition, Dissolution Rate, Permeation & Tissue Interaction
Impact of dissolution on pharmacokinetics

Performance Attributes – Dissolution Rate
- Clinical Impact

- Nebulized AZD5423 (VMD 1.3 & 3.1 μm)

- Same formulation
- Same nebulizer
- Same delivered dose
- Same lung dose
- Same regional deposition
- Different material
  - Different Dissolution Rate
  - Non-bioequivalent products

Conclusions

• *In vitro* dissolution methods for OIDP are attracting significant attention as dissolution appears to be important for some API/formulations

• Biorelevant testing combined with computer modelling enables a mechanistic understanding of inhalation biopharmaceutics, i.e. the fate of inhaled aerosols/drug in the lungs

• SimInhale COST ACTION MP1404 has enabled industry-academic collaboration to significantly advance this approach