Importance of Dissolution and Drug Release Testing

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Outline

• Importance of Dissolution
• Biowaiver → Reducing regulatory burden
• Progressive application of dissolution:
  Dissolution – BCS – BDDCS
• Drug Release - Novel dosage form
• Product quality and product performance test
• Predictive drug dissolution / simulation
• Biorelevant – Clinically Relevant - to QC !!!
• Clinically relevant specifications →
  Patient-focused Quality Standards
Dissolution Test

• It is the most useful single physicochemical test for assessment of drug product quality and drug product performance

• To assess batch to batch quality

• The release specifications (QC test) allows batch release into the market place and assures product performance

• Functions as a signal of BioInequivalence
Dissolution Related Guidances

- IR Dissolution Guidance
- ER (IVIVC) Dissolution Guidance
- BCS (Waiver) Guidance
- General BA/BE Guidance
- SUPAC Guidances (IR, MR, SS)
- IR / HS drug substance / Dissolution Guidance
- Product Specific (draft) guidances with IVRT

http://www.fda.gov/cder/guidance/index.htm
Dissolution and Drug Release Tests

• General Chapters in USP
  
  <701>  Disintegration
  <711>  Dissolution
  <724>  Drug Release
  <1092>  The Dissolution Procedure: Development and Validation
  <1094>  Capsules – Dissolution Testing and Related quality Attributes
  <1724>  Semisolid Drug products – Performance Tests
Dissolution Guidance

• Provides recommendations on the development of dissolution / drug release test methodology, approaches for setting specifications and the regulatory applications

• Provides methods for dissolution profile comparison and indications as to when dissolution is sufficient for biowaivers
Dissolution Test

• Mild enough to detect manufacturing and process variables that may affect in vivo performance of the product

• Should not be overly discriminative

• Basket (100 rpm) or Paddle (50-75 rpm) in 500-1000 mL of aqueous medium

• Use of surfactant with justification
New and Generic Medicines

• **New Medicines (NDA)**
  – Based on the experience gained during the drug development process and in vivo performance of appropriate test batches
  – Based on acceptable clinical, pivotal bioavailability and/or bioequivalent batches

• **Generic Medicines (ANDA)**
  – Generally the same as first entry (pioneer) drug product
  – Based on the acceptable bioequivalent batch
Dissolution Specifications

Immediate Release Drug Products

- **Single Point**
  - For routine quality control test

- **Two Points**
  - For characterizing the quality of the drug product (also for use as a QC test)

- **Profile**
  - Profile comparison for granting biowaivers
  - For accepting product “sameness” under scale-up and post-approval changes
Dissolution of Poorly Water Soluble Drugs in Oral Dosage Forms

Use of Surfactants
with Justification

(Lowest amount of surfactant must be used)
Dissolution – Gelatin Capsules

• Capsules – Pellicle formation due to cross linking
• Use and selection of enzyme (2\textsuperscript{nd} tier) based on pH of the dissolution medium (dm)
• Dissolution medium with pH equal or below 4.0
  Enzyme pepsin – activity of NMT 750,000 U/L of the dm.
• Dissolution medium with pH above 4.0 and below 6.8.
  Enzyme papain – activity of NMT 550,000 U/L of the dm
  or bromelain – activity of NMT 30 GDU/L of dm.
• Dissolution medium with pH equal or above 6.8. Enzyme:
  pancreatin – activity of NMT 2000 U/L of the dm.
• Pre-soaking with enzyme – if surfactant is in the dm.
Extended Release Drug Products

• **Profiles**
  – In multimedia, different pHs
  – Influence of agitation

• **Specifications**
  – Profiles with at least 3 to 4 points
  – Range of dissolution at all points
  – Time: 1 or 2 Hrs, around 50 % dissolution and around 80% dissolution
Progressive Application of Dissolution

Dissolution

Quality Control

SUPAC

Biowaiver

BCS → BDDCS
Progressive Application of Dissolution and Related Concepts

- **Process / Steps**
  - Drug release, Dissolution
  - Solubility, Permeability, Dissolution
  - Drug Disposition, Effect on transporters

- **Test / Concept**
  - 1975 Dissolution test
  - 1995 Biopharmaceutics Classification of Drugs (G. Amidon, et. al.)
  - 2005 Biopharmaceutics Drug Disposition Classification System (Wu and Benet)

- **Impact**
  - 1975: Process control, Batch-to-batch Quality control, Quality assurance, SUPAC related changes – Assurance of product sameness
  - 1995: Biowaiver for BCS Class 1 Drugs (FDA, 2000), Biowaiver for BCS Class 1, 3 and Weak Acids (WHO, 2006)
  - 2005: Predict Drug Metabolism, Drug Transport-Enzyme interplay, Potential Drug-Drug interaction in the intestine and liver

Dissolution

• Dissolution testing remains one of the pharmaceutical industry’s most straight forward, least expensive QC tools to assure product performance.

• Dissolution test distills all the information that is known about the performance of a pharmaceutical product in a laboratory setting.

• Research is now focused on ways to extend and improve IVIVC and make real-time release testing reality.

• Research in computer simulation, PBPK modeling and predictive in vivo dissolution is on the rise.
Dissolution Related Guidance

FDA Guidance for Industry:

• Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solids Oral Dosage Forms based on a Biopharmaceutics Classification System. December 2017

Dissolution Guidance
(IR HS Drug Substance)

• IR products with **highly soluble drug substance**
• Standard release test and criteria may be used in lieu of extensive method development and acceptance criteria-setting exercises.
• Establishes standard dissolution methodology and acceptance criteria for highly soluble drug substances.
• No requirement to show discriminatory ability of the dissolution method for drug products with HS drug substance.
• Follow BCS guidance to establish that the drug product contains highly soluble drug substance.
• Replaces draft dissolution guidance (for BCS 1,3) of Aug 2015.
• Drug substances that are not highly soluble, follow the recommendations in August 1997 dissolution guidance.
Dissolution Guidance
(IR HS Drug Substance)

- Applicable to solid orally administered IR drug products such as tablets and capsules.
- **Not** applicable for orally disintegrating tablets (ODT)*
- **Not** applicable to sublingual dosage form*
- **Not** applicable to NTI drugs
- May be applicable to chewable tablets if the dissolution studies are conducted on the intact tablets and the product meets the conditions described in the guidance.

* This guidance can be applicable, if the absorption from the oral cavity can be ruled out.
Dissolution Guidance
(IR HS Drug Substance)

Standard Dissolution Testing Conditions

• Basket Method (USP apparatus 1)
  – Stirring rate = 100 rpm
  – 500 ml. of 0.1N HCl in aqueous medium (900 ml with justification)
  – No surfactant in medium
  – 37 ± 0.5°C

• Paddle Method (USP apparatus 2)
  – Stirring rate = 50 rpm (75 rpm with justification)
  – 500 ml. of 0.1N HCl in aqueous medium (900 ml with justification)
  – No surfactant in medium
  – 37 ± 0.5°C

• Dissolution Acceptance Criteria
  – Q = 80% in 30 minutes
Dissolution Based Biowaivers

• **Conventional Release Products**
  - Lower strengths, proportional formulations, dissolution profile comparison, $f_2$
  - Drug products with highly soluble drug substances (BCS)

• **Extended Release Products**
  - Lower strengths, proportional formulations and same release mechanism
  - Beads in a capsule - Profile comparison in one medium
  - Tablets - Profile comparison, pH 1.2, 4.5, 6.8
Pharmaceutical Dosage Forms

• Traditional solid oral dosage forms → **dissolution test** e.g., tablets, capsules, suspensions

• Novel dosage forms → **In vitro release test** e.g., transdermal, semisolids, liposomes, stents, implants, inhalation products,
Dosage Form Tests

• **Product Quality Test**
  
  Intended to assess attributes such as assay, content uniformity, pH, minimum fill, microbial limits

• **Product Performance Test**
  
  Designed to assess product performance and in many cases relates to drug release from the dosage form.
Pharmaceutical Dosage Forms

- Oral – Dissolution test
  - Tablets, capsules, suspension
- Topical – Drug release test
  - Semisolids: cream, ointment, gel
- Parenteral – Drug release test
  - Liposomes, microspheres, emulsion
- Mucosal – Drug release test
  - Suppositories, medicated gum
- Inhalation – Particle size distribution and dissolution (!)
## Dosage Form Taxonomy (USP)

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Intended site of release</th>
<th>Dosage Form Examples</th>
<th>Dosage Form Quality Tests</th>
<th>Dosage Form Performance Tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parenteral</strong></td>
<td>Body tissues and fluids</td>
<td>Injectables, Liposomes, micro and nano particles, implants, stents</td>
<td>&lt;1&gt;</td>
<td>&lt;1001&gt;**</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td>Gastro intestinal tract</td>
<td>Tablets and capsules, liquids</td>
<td>&lt;2&gt;</td>
<td>&lt;701&gt;, &lt;711&gt;</td>
</tr>
<tr>
<td><strong>Topical / Transdermal</strong></td>
<td>Skin</td>
<td>Semisolids, TDS</td>
<td>&lt;3&gt;</td>
<td>&lt;724&gt;, &lt;1724&gt;</td>
</tr>
<tr>
<td><strong>Mucosal</strong> (Local or Systemic)</td>
<td>Mouth, eye, ear, rectum, vagina, intra-uterine</td>
<td>Films, tablets, liquids, suspensions, suppositories</td>
<td>&lt;4&gt;</td>
<td>&lt;1004&gt;**</td>
</tr>
<tr>
<td><strong>Inhalation</strong></td>
<td>Nasal cavity, lung</td>
<td>Liquids, aerosols, powders</td>
<td>&lt;5&gt;</td>
<td>&lt;601&gt;, &lt;602&gt;, &lt;603&gt;, &lt;604&gt;, &lt;1601&gt;</td>
</tr>
</tbody>
</table>

*Tests indicate the specific tests used for each dosage form, with numbers referring to specific USP chapters or sections for more detailed information.
Role of Dissolution Testing in Regulating Pharmaceuticals

- Increasingly, in vitro dissolution testing is relied on to assure product performance.

- An appropriate dissolution test procedure is a simple and economical method that can be utilized effectively to assure acceptable drug product quality.

- Appropriate dissolution test can be used as a surrogate marker for BA/BE.
Moving on …

in the Field of Dissolution Testing


• Clinically relevant dissolution specs – PB/PK modeling/DT

• Predictive dissolution / simulation to assure therapeutic efficacy and safety – biopredictive dissolution testing

• QbD/Design Space – critical product attributes
### Oral drug products

**BCS**

- High Permeability
  - High Solubility
    - BCS class 1
- Low Permeability
  - High Solubility
    - BCS class 3

### Topical drug products

**TCS**

- High Permeability
  - Low Solubility
    - BCS class 2
- Low Permeability
  - Low Solubility
    - BCS class 4

- Q1, Q2 Same
  - Q3 Same
    - TCS class 1
- Q1, Q2 Different
  - Q3 Same
    - TCS class 3
- Q1, Q2 Different
  - Q3 Different
    - TCS class 4

### Biowaiver

- ↑ Biowaiver
- ↑ BE
- ↑ Biowaiver
- ↑ BE

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Importance and Role of Dissolution Testing

• Increasingly in vitro dissolution testing is relied on to assure product performance

• An appropriate dissolution test procedure is a simple economical method that can be utilized effectively to assure acceptable drug product quality.
Conclusions

• Dissolution test has emerged as a most useful physicochemical test for assessment of drug product performance.

• Dissolution test is a biowaiver tool for reducing regulatory burden and maintaining drug product quality.
Thank You for Your Attention