Evaluation of Drug Product Performance
Dissolution Method Development and Regulatory Requirements

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Implementation of Biowaivers based on Biopharmaceutics Classification System

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Dissolution Test

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

• To assess batch to batch quality

• The release specifications (QC test) allows batch release into the market place

• Functions as a signal of BioInequivalence
Dissolution Test

• Mild enough to detect manufacturing and process variables that may affect in vivo performance of the product
  • Should not be overly discriminative
Dissolution

- Drug → Solubility
  - Immediate Release Dosage Form
  - Delayed Release Dosage Form
  - Extended Release Dosage Form
- Formulation
- Apparatus → Basket Method
  - Paddle Method
  - Other Methods
- Dissolution Medium → Aqueous Medium, pH
  - Type and Amount of Surfactant
  - Agitation
- Dissolution Sampling Times → One time, two times, or multiple times with profile.
Dissolution - *In Vitro* Release

Apparatus:

- Standard dissolution apparatus
  - Apparatus 1: Basket
  - Apparatus 2: Paddle
  - Apparatus 3: Reciprocating Cylinder
  - Apparatus 4: Flow-through
  - Apparatus 5: Paddle over Disk (Essentially same as Paddle)

- Need to avoid unnecessary proliferation of dissolution apparatus
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 for drug approval (12 units)
  - Profile comparison for biowaivers
  - For accepting product “sameness” under scale-up and post-approval changes
Extended Release Drug Products

- **Profiles**
  - In multimedia, different pHS
  - Influence of agitation

- **Specifications** (12 Units)
  - 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
DISSOLUTION PROFILE OF A CONTROLLED RELEASE PRODUCT

% DISSOLVED

TIME (HOURS)
Policy Related Dissolution, BA/BE and SUPAC Guidelines

• IR Dissolution Guidance
• ER (IVIVC) Dissolution Guidance
• BCS (Waiver) Guidance
• General BA/BE Guidance
• SUPAC-IR Guidance
• SUPAC-MR Guidance

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
Dosage Form Tests

• **Product Quality Test**
  
  Intended to assess attributes such as identity, strength, purity, 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.
Dissolution Testing of Poorly Water Soluble Actives in Oral Dosage Forms
Dissolution of Poorly Water Soluble Actives in Oral Dosage Forms

• Use of Surfactants
  – Why? What is Alternative?
• Types of Surfactants
• Methodology
  – Justification for surfactant use
  – Lowest amount of surfactant must be used
Surfactants

- Sodium Lauryl Sulfate (SLS)
- Sodium Dodecyl Sulfate (SDS)
- Labrasol
- Polysorbate 20
- Polysorbate 80
- Brij-35
- Triton X – 100
- POE 10 – Lauryl Ether
- N,N-dimethyldodecylamine-N-oxide
- HDTMA (CTAB)
Use of Surfactants for Poorly Water Soluble Drug Products

• Dissolution using Bile Acid and Bile Salts and Surfactants
CARBAMAZEPINE

IN VITRO - IN VIVO CORRELATION

IN-VIVO BIOAVAILABILITY

Dissolution Profile

MCG/ML

<table>
<thead>
<tr>
<th>Compound</th>
<th>Symbol</th>
</tr>
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<tbody>
<tr>
<td>Ciba</td>
<td>-</td>
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<tr>
<td>PBI-I</td>
<td>-</td>
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<tr>
<td>PBI-II</td>
<td>-</td>
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<tr>
<td>PBI-III</td>
<td>-</td>
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200 mg Dose

HOURS

% DISSOLVED

1% aqueous SLS Paddle-75rpm

MINUTES
WATER INSOLUBLE DRUG: DANAZOLE 200 MG CAP
DISSOLUTION IN PRESENCE OF SLS

% DISSOLVED

TIME (MINUTES)
PADDLE 75 RPM IN DIFFERENT MEDIA

1.0% SLS/W  0.25% SLS/W
0.75% SLS/W  0.1% SLS/W
0.5% SLS/W  pH 7.4

% DISSOLVED

TIME (MINUTES)
PADDLE 75 RPM, 0.75% SLS/W.

- STERLING 50 MG  - STERLING 200 MG
- STERLING 100 MG  - AM. THER. 200 MG
Dissolution of Capsules

Soft Gelatin and Hard Gelatin Capsules
Dissolution – Gelatin Capsules

- Capsules – Pellicle formation due to cross linking
- Use and selection of enzyme (2nd 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.

- 2-step Tier II method for poorly soluble drugs using surfactant media. Pre-soaking with enzyme – if surfactant is in the dm.
**In Vitro** Dissolution

*In Vitro* dissolution is a good QC test because there are few, if any, examples where a product passes dissolution but fails bioequivalence.

However, there are examples where products are BE, but have different dissolution characteristics.
Primidone 50 mg

Dissolution and Plasma Level Profile

% Dissolved

NEW MYSOLIN

OLD MYSOLIN

Water, Paddle 50 rpm

Time (minutes)

μg/ml

SUSPENSION

OLD MYSOLIN

NEW MYSOLIN

Time (hours)
Dissolution in Alcohol Media
ER Products - Dissolution Studies in Alcohol

- Due to concerns of dose dumping when taken with alcohol, additional dissolution testing using various concentrations of ethanol in the dissolution medium is required:
  - T and R product, 12 units in each case,
    - data collected every 15 minutes for 2 hours
- Proposed method (without alcohol)
  - 5% (v/v) alcohol
  - 20% (v/v) alcohol
  - 40% (v/v) alcohol

(e.g., Morphine, Cyclobenzaprine, Methylphenidate HCl, Dexamethylphenidate HCl, Oxycodone, Trazodone, Bupropion, Venlafaxine, Lamotrigine, Quetiapine Fumarate, Ropinirole)
Dissolution Test

• *In Vitro Quality Control Dissolution Test*

Dissolution test procedure identified in the pharmacopeia, generally a one time point dissolution test for immediate release products and 3 or more time points dissolution test for modified release products.

• *In Vitro Equivalence Test*

In vitro equivalence test is a dissolution test that includes dissolution profiles comparison between the multisource product and the comparator product in three media: pH 1.2, 4.5 and 6.8.

Dissolution Profile Comparison
Dissolution Profile Comparison

\[ f_1 = \left\{ \left[ \sum_{t=1}^{n} R_t - T_t \right] / \left[ \sum_{t=1}^{n} R_t \right] \right\} \cdot 100 \]

\[ f_2 = 50 \cdot \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \right\} \cdot 100 \]

- \( R_t \) and \( T_t \) are the cumulative % dissolved at each of the selected \( n \) time points

- \( f_1 \) is proportional to the average difference between the two profiles (difference factor)

- \( f_2 \) is inversely proportional to the average squared difference between the two profiles and measures the closeness between the two profiles (similarity factor).
Dissolution Profile Comparison

- Regulatory interest is to know how similar the two curves are, and for this reason, the $f_2$ comparison has been the focus in Agency guidances.

- When the two profiles are identical, $f_2=100$. An average difference of 10% at all measured time points results in a $f_2$ value of 50. FDA has set a public standard of $f_2$ value between 50-100 to indicate similarity between two dissolution profiles.
Dissolution Profile Comparison

- At least 12 units should be used for each profile determination. To use mean dissolution data, the % cv at the earlier point should not be more than 20% and at other time points should not be more than 10%.

- The dissolution measurements of the two products (test and reference, pre- and post- change, two strengths) should be made under the same test conditions. The dissolution time points for both the profiles should be the same, e.g., for IR products 15, 30, 45 and 60 minutes, for ER products 1, 2, 3, 5 and 8 hours.

- Because $f_2$ values are sensitive to the number of dissolution time points, only one measurement should be considered after 85% dissolution of the product.
Dissolution Profile Comparison

- For products which are rapidly dissolving, i.e., more than 85% in 15 minutes or less, a profile comparison is not necessary.

- A $f_2$ value of 50 or greater (50-100) ensures sameness or equivalence of the two curves and, thus, the performance of the two products.

- For circumstances where wide variability is observed, or a statistical evaluation of $f_2$ metric is desired, a bootstrap approach to calculate a confidence interval can be performed.
FDA: New Drugs
Setting Dissolution Specifications

General Strategy
- Focus on mean
- Variability
- IVIVC?
- Quality problem
  - Degradation?
  - Stability?
  - Formulation?

Problem Solving

Setting Specification

Risk Based Evaluation
- Assess and manage risk
- Risk informed decision making

Current Practice
- Clinical and biobatch
- Discriminating dissolution method
- Completeness

Adapted from John Duan/FDA presentation at USP on 3/25/2014
Risk Informed Decision Making

• Risk Assessment
  – What can go wrong?
  – What is the likelihood it would go wrong?
  – What are the consequences?
  – What is the chance to detect?

• Knowledge Inventory
  – What information will be most useful
  – What knowledge is already available
  – What information is not available

Adapted from John Duan/FDA presentation at USP on 3/25/2014
Generic Drugs: Regulatory Dissolution Method

Immediate release and Delayed Release Products

• Generally USP method, which is most of the time same as NDA method.
• FDA recommended method published in FDA data-base

Extended Release Products

• Based on Biobatch
• It can be different from manufacturer to manufacturer. OGD tries to achieve consistency in selecting dissolution methods for generic extended-release (ER) products
• In Quality by Design (QbD) paradigm, it may be necessary to develop dissolution method for ER products case-by-case basis
Root Causes of Dissolution Changes

• Stability
  – Slow down,
  – Increase in variability

• Quality problem
  – Chemical degradation,
  – Formulation change,
  – Manufacturing process,

• Gelatin cross linking
  – Nature of the drug,
  – Excipients (corn starch contains stabilizer),

• Storage conditions
  – Heat and humidity
Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, $f_2$
  - BCS Class 1: HS/HP/RD
  - BCS Class 2: LS/HP, Weak acids, HS in pH 6.8
  - BCS Class 3: HS/LP/Very Rapidly dissolving

- **Extended Release Products**
  - Lower strengths, proportional formulations and same release mechanism
  - Beads in a capsule - Profile comparison in one medium
  - Tablets - Profile comparison in pH 1.2, 4.5, 6.8
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.
Dissolution Science

Where are we today?

• Increased knowledge and understanding of the science behind the test methodology

• Availability of precise, rugged and reliable dissolution test equipment

• Dissolution test is used as a surrogate in vitro bioequivalence test and

• Biowaiver criteria are set based on dissolution profile comparison.
Role of Dissolution

Where is it used?

- Development of the dissolution test as a QC test
- QC test for various dosage forms: IR and ER
  - Biopharmaceutics Classification System
  - IVIVC
- Profile and profile comparison
  - Biowaiver (Proportionally Similar, IR and ER)
  - SUPAC related changes
Dissolution Test
Impact

• Assures Product Quality
• Useful as a Bioequivalence Test
• Establishes Procedure for Granting Biowaiver
  - New Drug Application and Abbreviated New Drug Application
  - Higher Strength
  - Lower Strength(s)
• Assures Product Sameness Under SUPAC Related Changes
Thank You For Your Attention