Role of Dissolution in Regulating Pharmaceutical Products

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Outline

• Dissolution
• Biowaiver
• SUPAC – IR, MR, SS
• Progressive application of dissolution: Dissolution – BCS – BDDCS
• Product Quality and Product Performance Tests
• Reducing regulatory burden: Increasing importance of dissolution
• Topical: Q1, Q2, Q3
• Novel dosage form
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
Policy Related Dissolution BA/BE Guidances

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

http://www.fda.gov/cder/guidance/index.htm
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)**
  - Based on the acceptable bioequivalent batch of the drug product
  - Generally the same as first entry (pioneer) drug product
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 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
Dissolution Guidance

• Provides recommendations on the development of dissolution 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
Test Conditions: Immediate Release Drug Products

- **Apparatus**
  - Apparatus 1 (Basket), 50/120 rpm
  - Apparatus 2 (Paddle), 50-75 rpm

- **Medium**
  - Aqueous Medium, pH 1.2 – 6.8
  - For sparingly water soluble drugs – use surfactant - must be justified, lowest amount must be used
  - 500-1000 ml at 37 ± 0.5°C

- **Sampling Times**
  - 15 minute intervals until 85 % dissolution
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 Testing of Poorly Water Soluble Drugs in Oral Dosage Forms

Dissolution of Poorly Water Soluble Drugs 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)
WATER INSOLUBLE DRUG: DANAZOLE 200 MG CAP DISSOLUTION IN PRESENCE OF SLS

PADDLE 75 RPM IN DIFFERENT MEDIA

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

PADDLE 75 RPM, 0.75% SLS/W.

- STERLING 50 MG
- STERLING 200 MG
- STERLING 100 MG
- AM. THER. 200 MG
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.
- 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
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., Oxycodone, Trazodone, Bupropion, Venlafaxine, Lamotrigine, Quetiapine Fumarate, Ropinirole)
Progressive Application of Dissolution

Dissolution

Quality Control

SUPAC

Biowaiver

BCS
Progressive Application of Dissolution and Related Concepts

Process / Steps
- Drug release, Dissolution

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

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

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

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

• Novel dosage forms → In vitro release test e.g., transdermal patches, semisolids, liposomes, stents, implants
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 (!)
Novel / Special Dosage Forms - Report

FIP/AAPS Joint Workshop Report: Dissolution / In vitro Release Testing of Novel / Special Dosage Forms:

- *Die Pharmazeutische Industrie*:

*FIP/RPSGB Workshop in London – October 20-21, 2008*
*AAPS/FIP Workshop in Los Angeles – November 7-8, 2009*
Progressively Reducing Regulatory Burden

Increasing Importance of Dissolution
Progressively Reducing Regulatory Burden

- **Tools**
  - BE Studies
  - Dissolution
  - In Vitro Drug release
  - Dissolution

**GENERIC DRUGS**
- Optimizing Product Performance
- Maintaining Product Quality

**ANDA / BE**
- IR and MR Biowaiver
- Semisolds Biowaiver
- IR - Optimum Bioavailability

**BCS**
- Lower strength
- Q₁, Q₂, Q₃ Lower strength

**Medicines Compendium**

Ref: VP Shah et.al., The AAPS Journal. 16: 621-624, 2014
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 Test
Impact

• Assures product quality
• Useful as a bioequivalence test
• Establishes procedures for granting biowaiver
  – New Drug and Abbreviated New Drug
  – Higher strength
  – Lower strength
• Assures product sameness under SUPAC
Conclusions

- Dissolution test has emerged as a most useful physicochemical test for assessment of drug product performance.
- Dissolution test is a biowaiver tool
- Dissolution test is a tool for reducing regulatory burden
Thank You for Your Attention