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 (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.
- 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

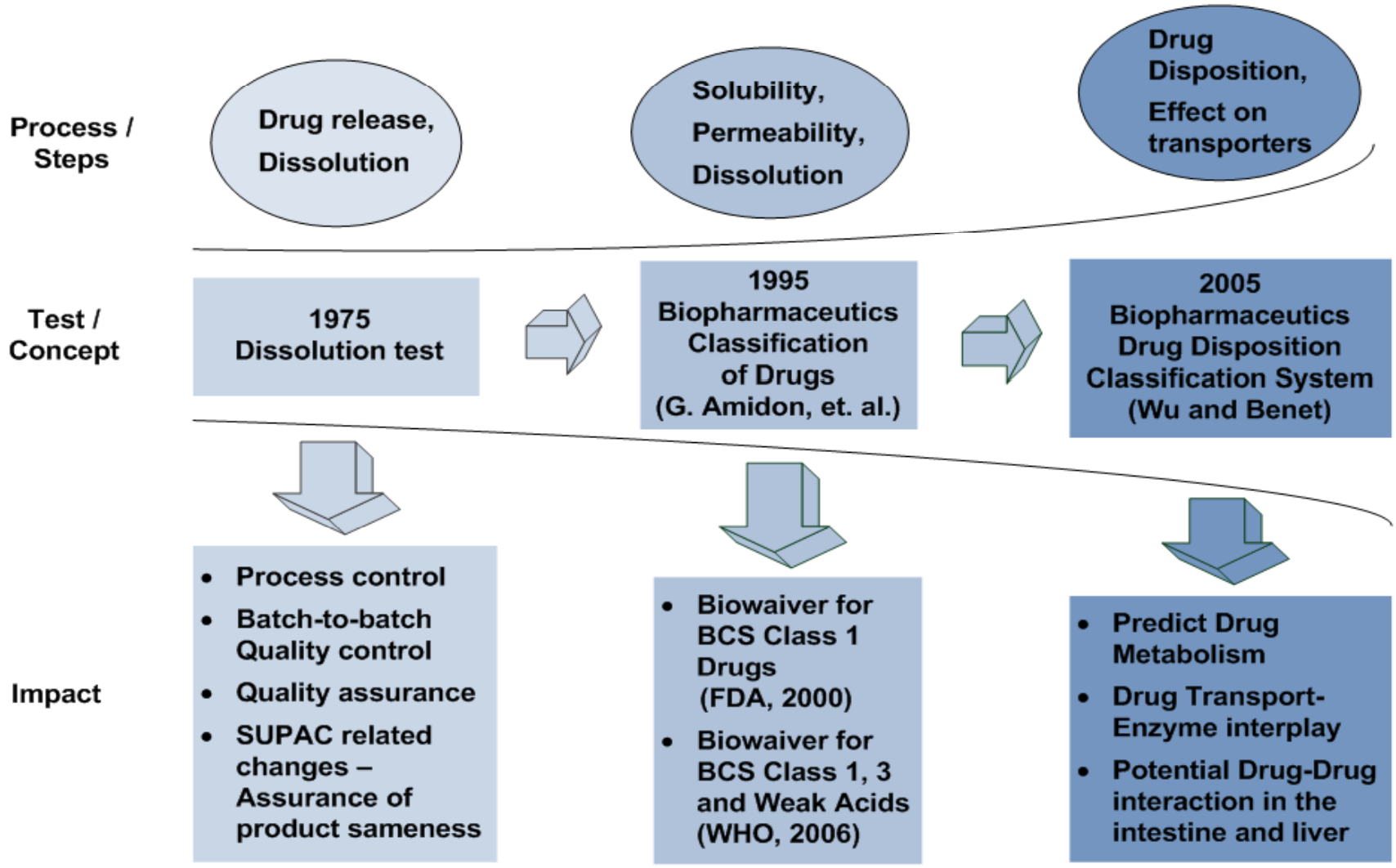
Quality Control

SUPAC

Biowaiver

BCS → BDDCS

Progressive Application of Dissolution and Related Concepts



Ref: VP Shah, J Pharm Sci. 102: 2895-7, 2013.

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 Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing **High Solubility Drug Substances**. August 2018.

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 $\pm$ 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 $\pm$ 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)

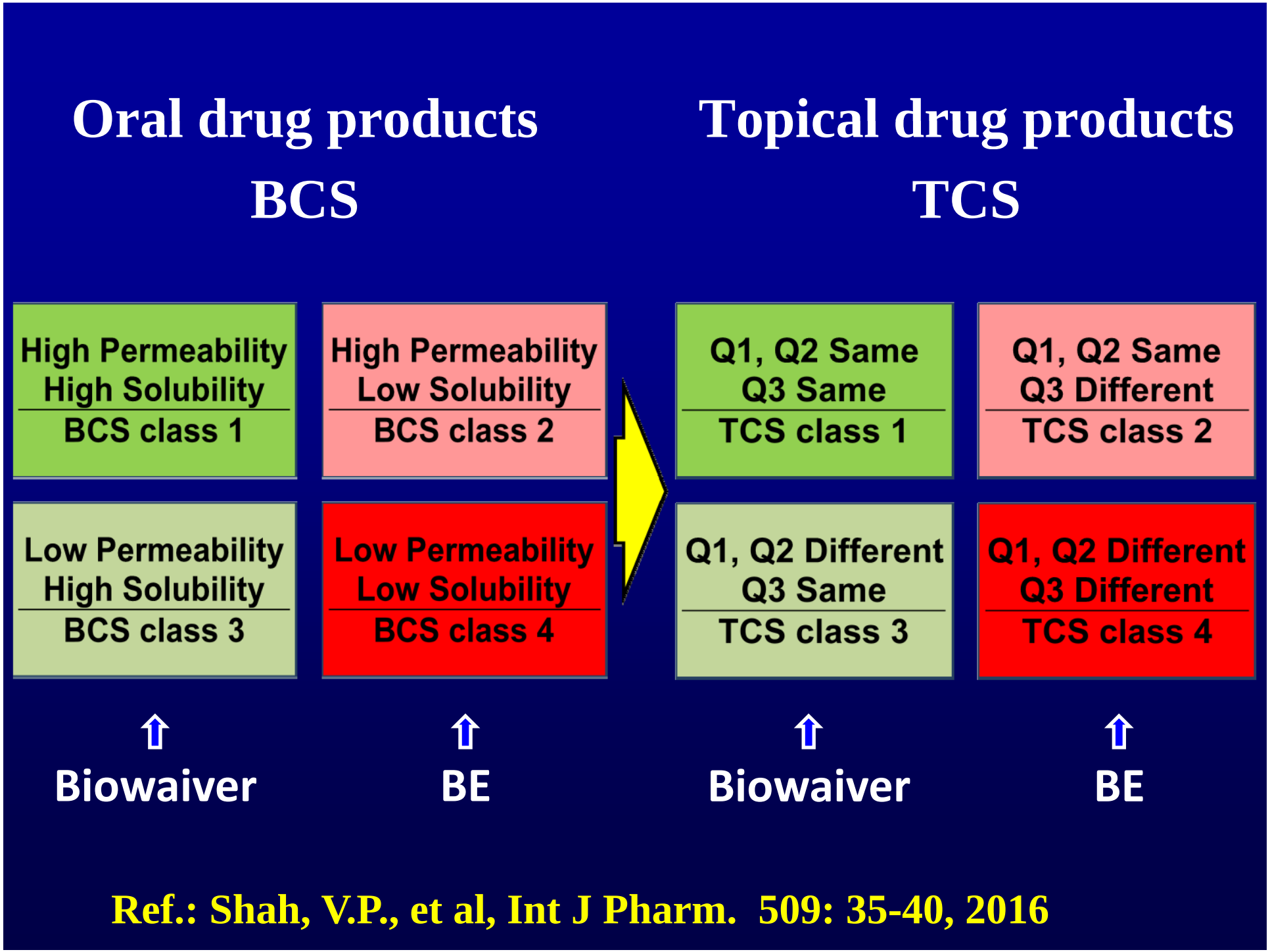
Route of Administration	Intended site of release	Dosage Form Examples	Dosage Form Quality Tests	Dosage Form Performance Tests*
Parenteral	Body tissues and fluids	Injectables, Liposomes, micro and nano particles, implants, stents	<1>	<1001>**
Oral	Gastro intestinal tract	Tablets and capsules, liquids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

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

- Workshop Report: Dissolution / In vitro release testing of novel / Special dosage forms: CK Brown et. al, *AAPS PharmSciTech:* Vol 12 (2), 782-794, 2011
- Workshop Report: Biorelevant in vitro performance testing of orally administered dosage forms: C Reppas et.al. *Pharm Res. 31:1867-1876, 2014.*
- 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



Ref.: Shah, V.P., et al, Int J Pharm. 509: 35-40, 2016

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