# Dissolution, BCS and Biowaivers

## Vinod P. Shah, Ph.D.
FIP/SIG Chair on Regulatory Sciences
Pharmaceutical Consultant

## 1st MENA Regulatory Conference on Bioequivalence, Biowaivers, Bioanalysis and Dissolution

Amman, Jordan.  September 23-24, 2013

# Outline

- **Background**

- **Dissolution**

- **Profile Comparison**

- **Biowaiver**

- **BCS**

- **Conclusion**

# Drug Products
## Drug Approval

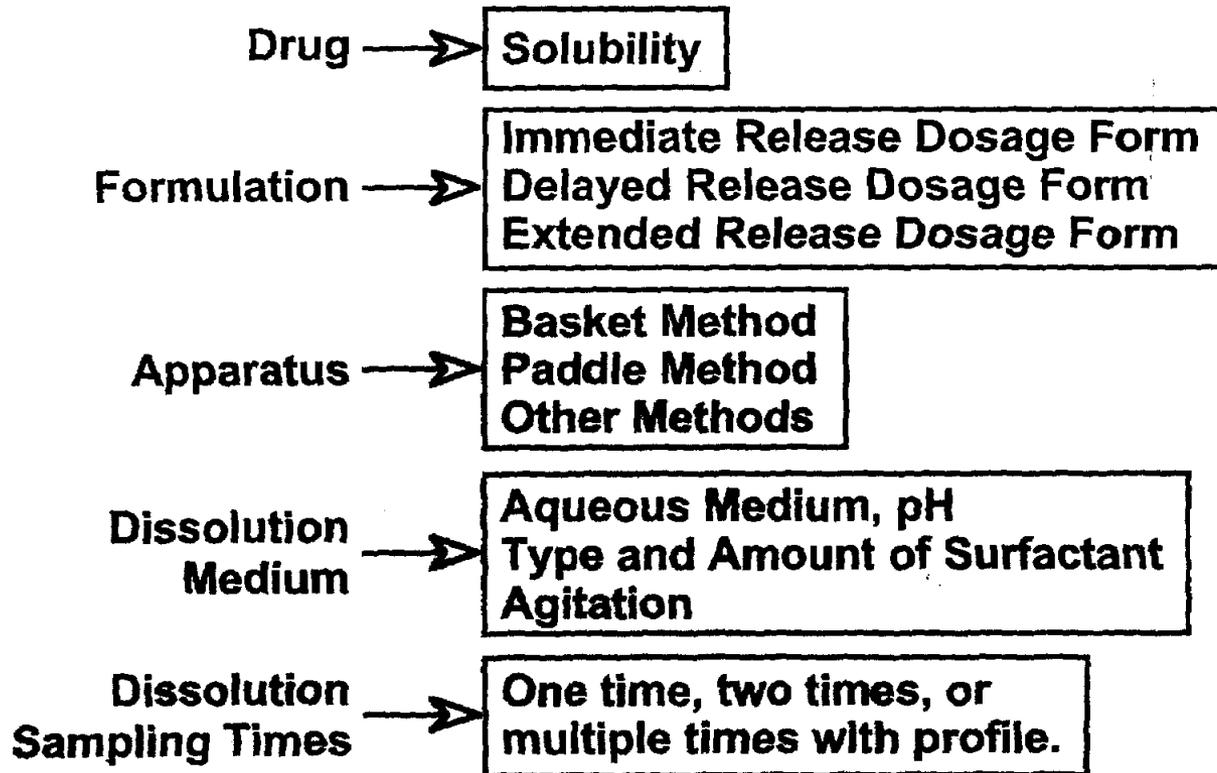| New Drug Application (NDA) | Abbreviated New Drug Approval (ANDA) |
|---|---|
| Safety: Toxicity Studies | |
| Efficacy: Clinical Studies<br><br>• Bioavailability Studies<br><br>• Pharmacokinetic studies | • Bioequivalence Studies |
| • Manufacturing Controls | • Manufacturing Controls |
| • *In Vitro* Dissolution | • *In Vitro* Dissolution |

# Drug Product Standards - Quality
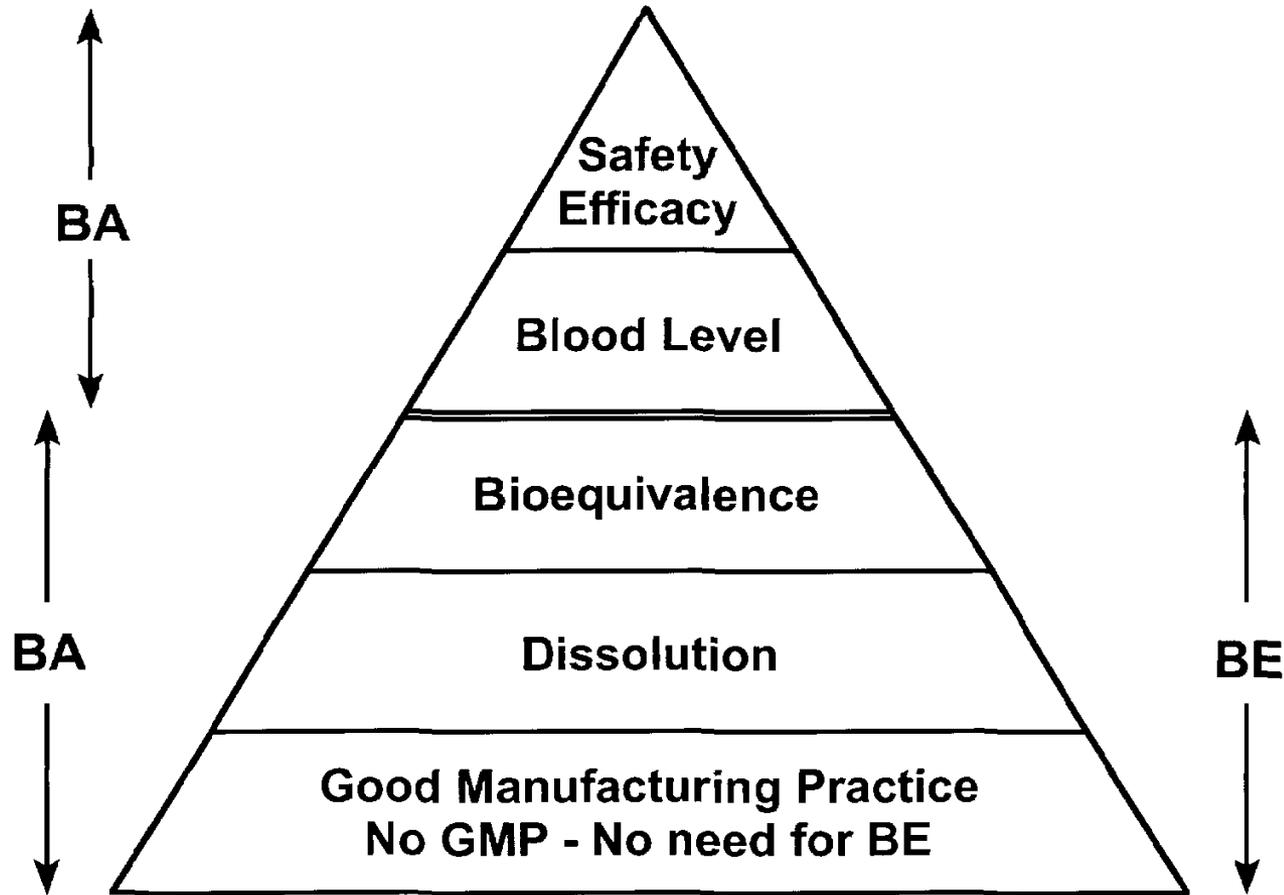
# Dissolution Test

- 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 |

Formulation ⟶ | Immediate Release Dosage Form
Delayed Release Dosage Form
Extended Release Dosage Form |

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. |

# 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

# 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 $\pm$ 0.5$^o$C
- **Sampling Times**
  - 15 minute intervals until 85 % dissolution

# Dissolution Data

## 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
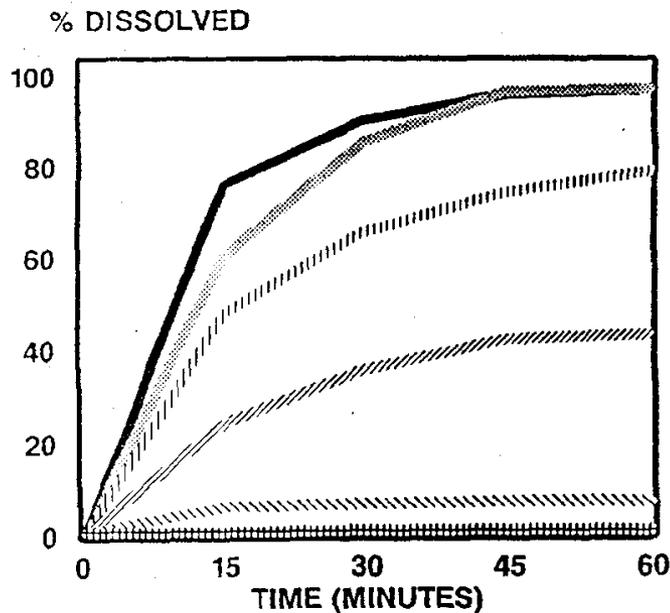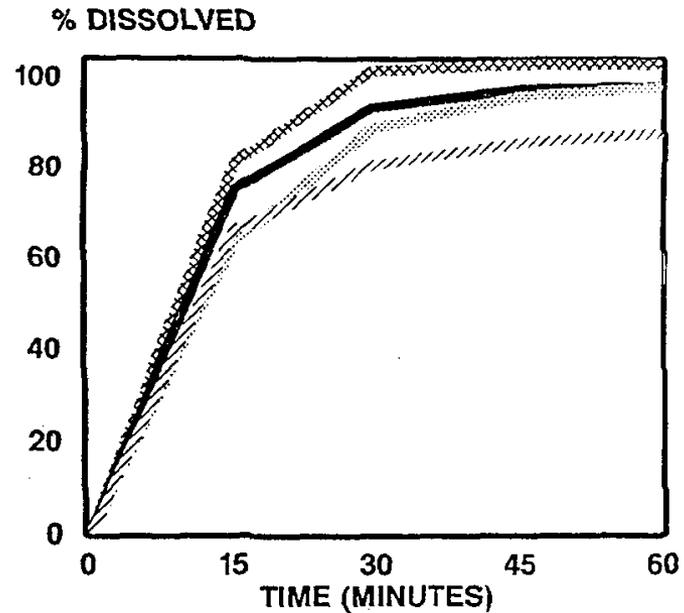
# Dissolution

## Sparingly Water Soluble Drug products

**Dissolution medium**

- Use of surfactant must be justified
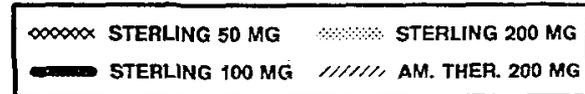
- Lowest amount of surfactant must be used.

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



% DISSOLVED

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

PADDLE 75 RPM, 0.75% SLS/W.

| | |
|---|---|
| ◇◇◇◇◇ STERLING 50 MG | ░░░░░ STERLING 200 MG |
| ━━━ STERLING 100 MG | /////// AM. THER. 200 MG |

# CARBAMAZEPINE
# *IN VITRO* - *IN VIVO* CORRELATION

### IN-VIVO BIOAVAILABILITY



MCG/ML

| | | Ciba |
|---|---|---|
| | ——— | PBI-I |
| | · · · · | PBI-II |
| | /////· | PBI-III |

200 mg Dose

HOURS
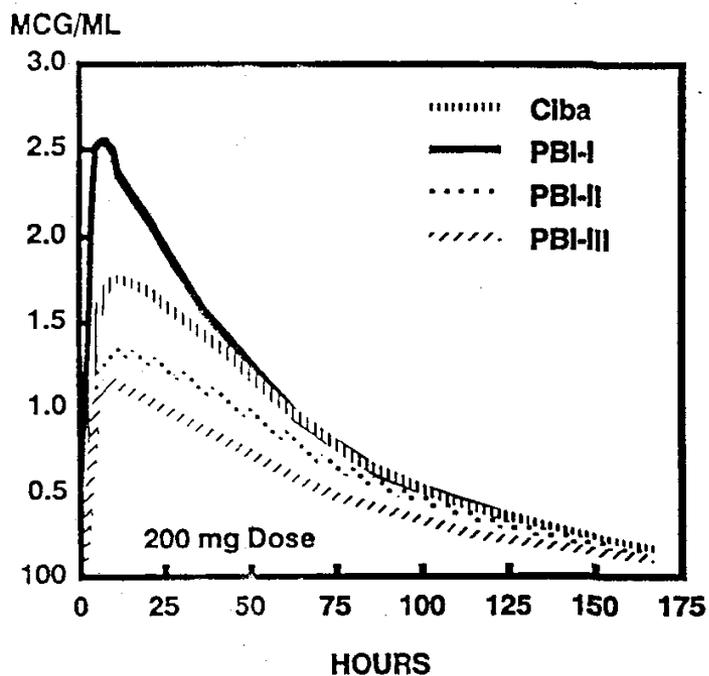
### DISSOLUTION PROFILE



% DISSOLVED

1% aqueous SLS  Paddle-75rpm

MINUTES
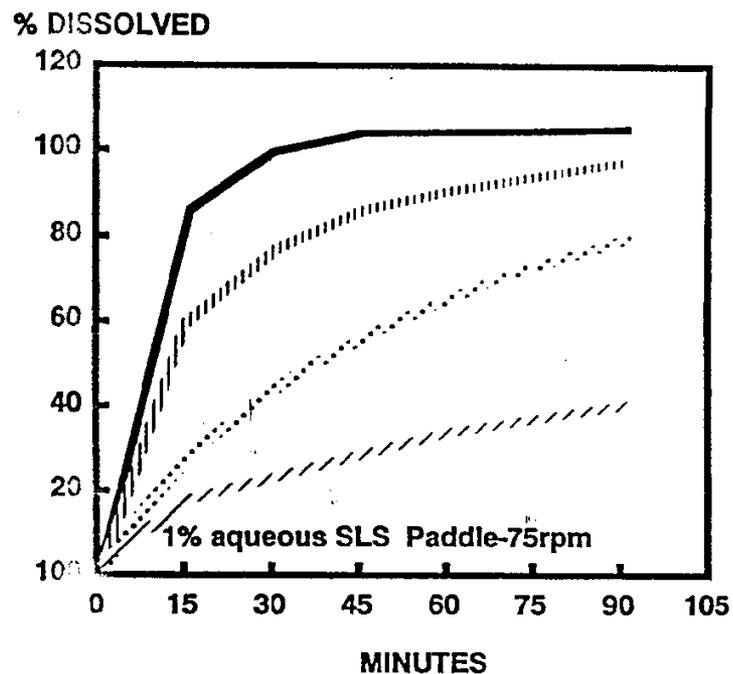
# Dissolution Guidance - IR Products

*Multiple Dissolution Media Test*

- **Gelatin Capsules**

  - **SGF without enzyme**

  - **SGF with Pepsin**

    OR

  - **SIF without enzyme**

  - **SIF with Pancreatin**

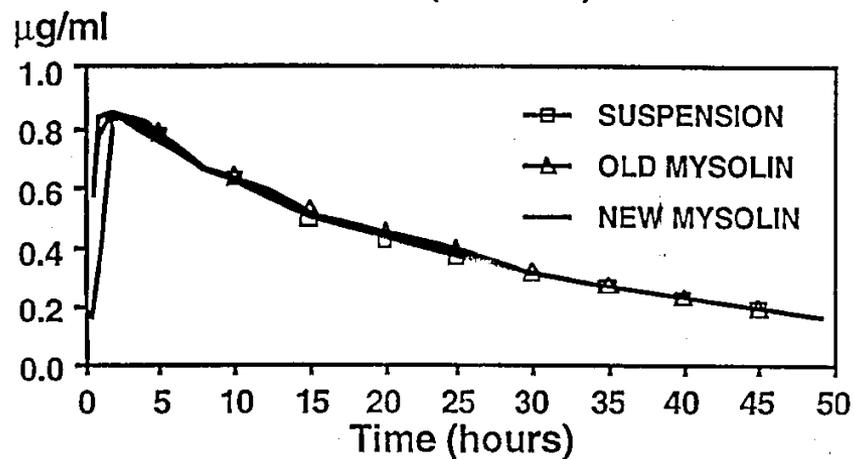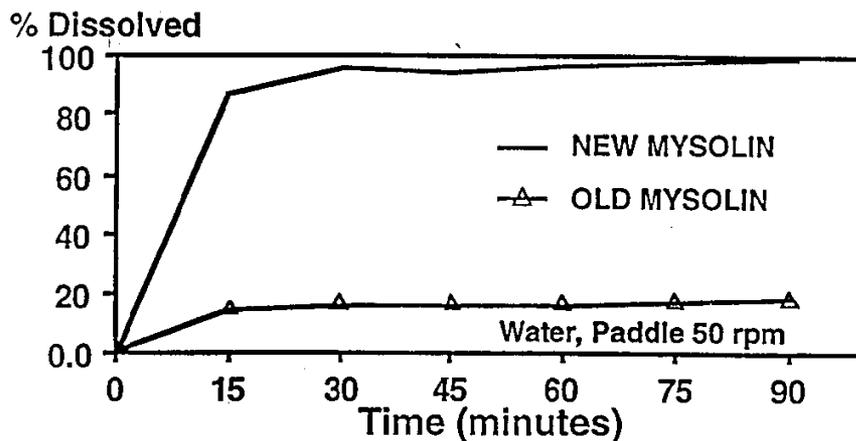- **To accurately reflect physiologic conditions of the GI tract.**

# *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 Data
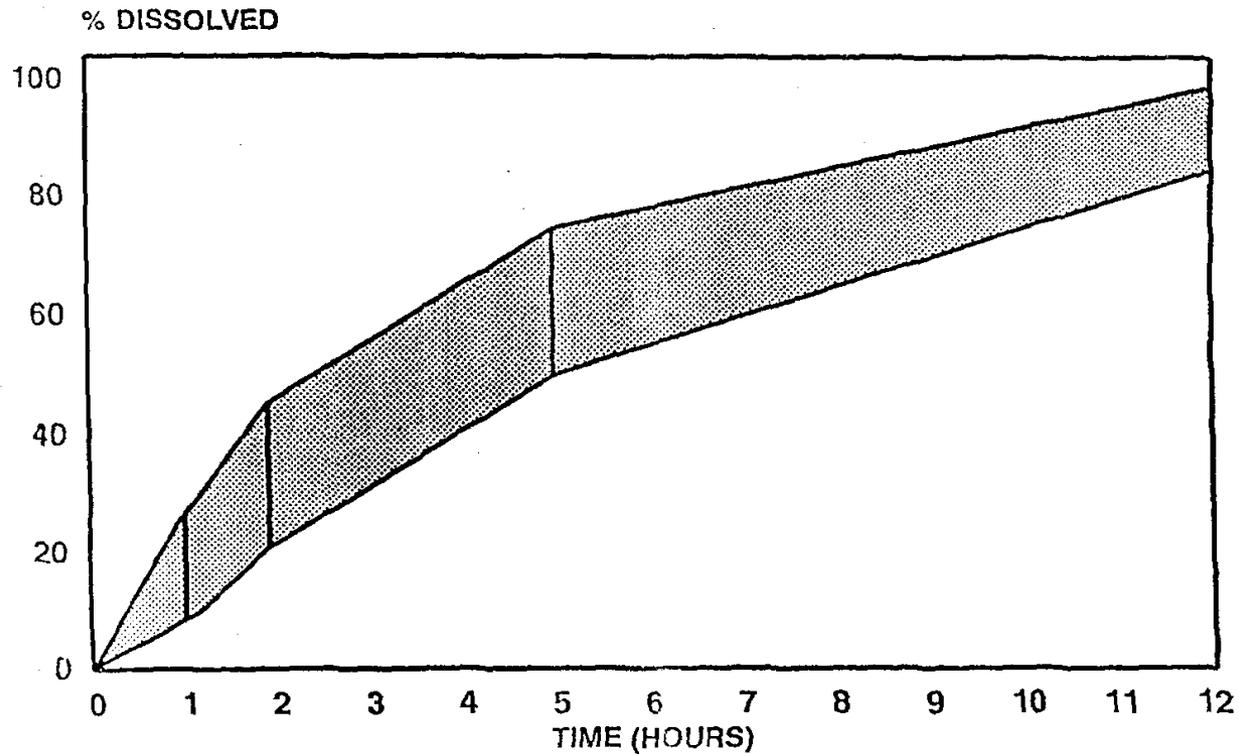# Extended Release Drug Products

- **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

# DISSOLUTION PROFILE OF A
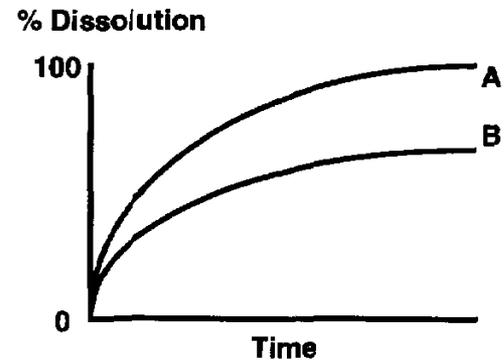# CONTROLLED RELEASE PRODUCT

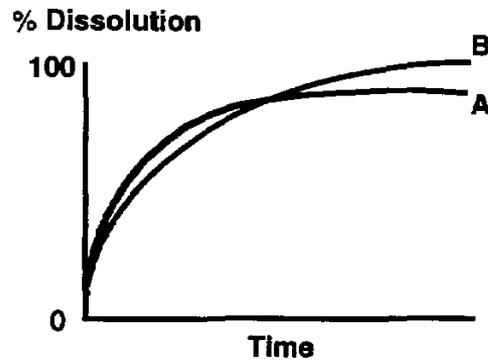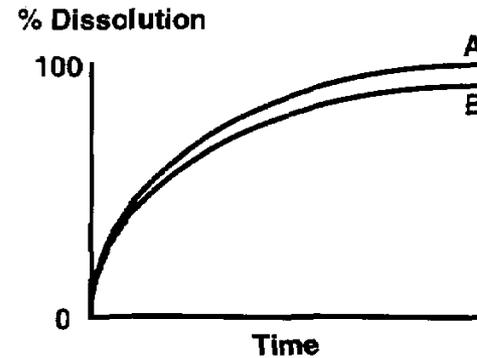# Policy Related Dissolution, BA/BE and SUPAC Guidances

- **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
# Profile Comparison

# Dissolution Profile Comparison

**Are These Profiles Similar?**
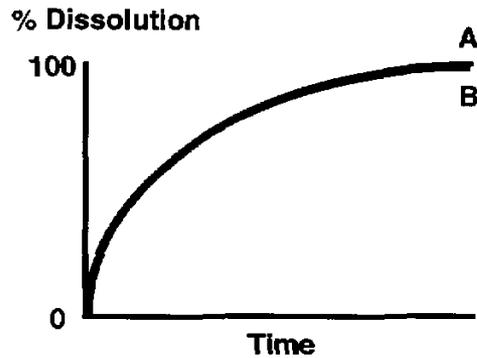
# Dissolution Profile Comparison

$$f_1 = \{[\textstyle\sum_{t=1}^{n} \mid R_t - T_t \mid ]/[\textstyle\sum_{t=1}^{n} R_t ]\} \bullet 100$$

$$f_2 = 50 \bullet \log \{[1+(1/n)\textstyle\sum_{t=1}^{n} (R_t - T_t)^2 ]^{-0.5} \bullet 100\}$$

- $R_t$ 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 f2 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.**

# Biowaivers

# Biowaivers

## Proportionally Similar

- All active and inactive ingredients are exactly in the same proportion

- Total weight remains nearly the same for all strengths (within ± 10% of total weight of the strength on which a biostudy was performed) and the change in strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.

# Immediate Release Drug Products

- Highest strength
  - approved based on BE study
    (unless API belongs to BCS class 1)
- Lower strengths
  - dose proportional formulations biowaiver based on dissolution profile comparison.

# Extended Release Drug Products

- Highest strength
  - approved based on BE study.

- Lower dose – Formulation proportional and same drug releasing mechanism
  – Beaded capsules: dissolution profile comparison with highest strength under one test condition
  – Tablets: dissolution profile comparison with highest strength in pH 1.2, 4.5 and 6.8

# BCS
# Biopharmaceutics Classification System

# Biopharmaceutics Classification System

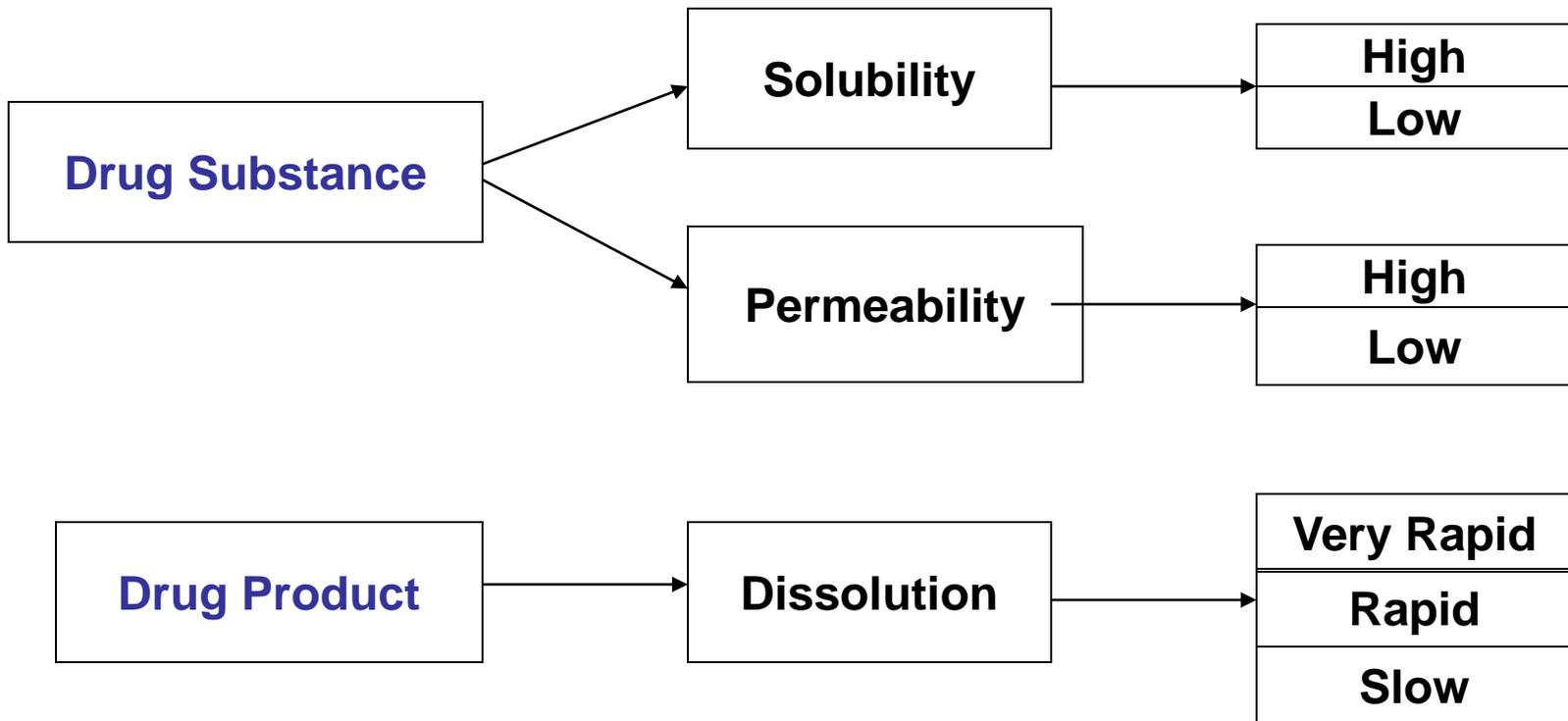• **BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, BCS takes into account three major factors that govern the rate and extent of absorption from IR solid oral dosage forms: dissolution, solubility and intestinal permeability.**
 **BCS Guidance:**

**IR drug products**
**non-NTI drug products**

# Biopharmaceutics Classification System

```
Drug Substance ─┬─→ Solubility ──→ High
                │                   Low
                │
                └─→ Permeability ──→ High
                                     Low

Drug Product ──→ Dissolution ──→ Very Rapid
                                 Rapid
                                 Slow
```

# Waiver of in vivo BA and BE for IR Products Based on BCS

- **BCS Class 1:**
  - **Highly Soluble** (Highest dose soluble in 250 ml in water over pH range of 1- 6.8
  - **Highly Permeable** (Extent of absorption greater than 85%)
  - **Rapidly dissolving** (Basket at 100 rpm, paddle at 50 rpm in 900 ml of pH 1.2, 4.5 and 6.8 buffer)

- **For a waiver of BE, the test and the reference product should exhibit similar dissolution profile, $f_2$ criteria**

# 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.

Ref: WHO Technical Report Series No. 937, 2006 Annex 7, p 347-390.

# Dissolution Test (BCS)

*Multisource (test) and*
*Comparator (reference) product*

- Paddle method at 75 rpm or
  Basket method at 100 rpm
- Dissolution profile in pH 1.2, 4.5 and 6.8
- Similarity $f_2 \geq 50$

# BCS Based Biowaivers*

- ## BCS Class 1: HS/HP
  - VRD or RD in pH 1.2, 4.5 and 6.8

- ## BCS Class 2: LS/HP/Weak Acids
  - Rapid dissolution in pH 6.8 and similar dissolution profile in pH 1.2, 4.5 and 6.8

- ## BCS Class 3: HS/LP/VRD
  -  contains no inactive ingredients that are known to alter GI motility and/or absorption

For biowaivers Test (multisource) and Reference (comparator) products must have similar dissolution profile ($f_2$) in all 3 media

Ref: WHO Technical Report Series No. 937, 2006 Annex 7, p 347-390.

# SUPAC
## Scale-Up And Post-Approval Changes

# 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

# Drug Product Quality Tests and Drug Product Performance Test

- Drug product tests are divided into two categories
  (1) Those that assess general quality attributes and
  (2) Those that assess product performance, i.e., in vitro release of the drug substance from the drug product.

- Quality tests assess the integrity of the dosage form, whereas performance test assess drug release and other attributes that relate to in vivo drug performance. Taken together, quality and performance tests assure identity, strength, quality and purity of the drug product.

# 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 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.

# Thank You for Your Attention