Use and Limitations of *In Vitro* Dissolution Testing: Topic Introduction and Overview

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Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012
In Vitro Dissolution Testing: Objectives

• Assure batch to batch quality
• Guide development of new formulations
• Provide “process control” and quality assurance
• Ascertain the need for bioequivalence studies
  – Different strengths
  – Post-approval changes
  – Multi-source products
Dissolution Testing: Issues

- Dissolution testing can be “non-discriminating”.
- Dissolution testing can be “over discriminating”.
- Products that dissolve about 70% in 45 minutes often have no medically relevant bioequivalence problems.
- Dissolution testing (especially only a single point criterion) is often not sufficient to assure product quality/ bioavailability.
- Demonstration of *in vitro-in vivo* correlation (IVIVC) is necessary.
- IVIVC’s are “Product Specific”.

3
Desired Future State of *In Vitro* Dissolution Testing

- Sensitive enough to detect relevant product changes so as to ensure the quality and consistent performance of products
- Predictive of *in vivo* performance of drug products and thus reduce unnecessary human studies, accelerate drug development, and hasten evaluation of post-approval changes
Uses and Limitations of *In Vitro* Dissolution Testing

- Use and Limitations of *In Vitro* Dissolution Testing: Topic Introduction and Overview
  - Lawrence Yu
- Dissolution Testing: Evolving Dissolution Apparatus
  - Cindy Buhse
- Dissolution Testing: Evolving Dissolution Media for Predicting *In Vivo* Performance
  - Arzu Selen
- Oral Bioperformance & 21st Century Dissolution Testing
  - Gregory Amidon
- Dissolution Testing and Quality-by-Design
  - Lawrence Yu
- Followed by:
  - Topic Wrap-up and Future Directions
  - Questions to the Committee/Committee Discussion
Dissolution Testing: Evolving Dissolution Apparatus

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

Cindy Buhse, Ph.D., Director
Zongming Gao, Ph.D., Chemist

Division of Pharmaceutical Analysis
Center for Drug Evaluation and Research
US Food and Drug Administration
Dissolution Testing Evolves from Disintegration Test

- Convenient and sensitive chemical analyses weren't available in 1950s.

- Official disintegration tests were adopted in 1945 by the British Pharmacopoeia and in 1950 by the USP.

- However, disintegration was recognized as an **incomplete test** as evidenced by the 1950 USP-NF statement that "disintegration does not imply complete solution of the tablet or even of its active ingredient".

*Stoll-Gershberg disintegration apparatus*

A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 – Basket Method

Basket Stirrer Method

Searl and Pernarowski, 1967

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.
A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 – Paddle Method

(A) Beaker Method

Levy-Hayes, 1960
A Proliferation of Designs for Dissolution Apparatuses between 1960 and 1970 -- Reciprocating Cylinder Method

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.
The First USP Dissolution Apparatus 1, Basket

**USP Apparatus 1**

*A – Basket*
*B – 1000ml resin flask*
*C – Cover*
*D – High-torque stirring motor*

1970 - Dissolution test, apparatus 1 (basket), USP 18
1976 - Dissolution test, apparatus 2 (paddle), USP 19

Belachew Desta, An evaluation of the USP dissolution apparatus, 1972, Thesis of the University of British Columbia.
Early Dissolution Testing in a FDA Lab in 1970s

USP rotating-basket apparatus and a centering tool

Kirchhoefer, Douglas, Wells, Furman, Cox, and Myrick

USP paddle apparatus

Pharmaceutical Technology, April, 1978, Vol 2, 16-53
FDA’s Definition and Views on Dissolution Testing in 1970’s

• *In vitro* dissolution testing as applied to solid-dosage drug forms measures the amount of drug dissolved in a known volume of liquid medium at a predetermined time, using a specified apparatus designed to carefully control the parameters of dissolution testing.

• *In vitro* dissolution testing can help pinpoint formulations that may present potential bioequivalence problem.

• Once a formulation has been shown to be bioavailable, dissolution testing is of great value in assuring lot-to-lot bioequivalence.

FDA’s Concerns and Standpoint on Dissolution Testing in 1970’s

- Dissolution tests are critical and difficult to carry out properly. Care and attention must be given to those aspects that have been identified as crucial. It is our hope that other scientists will share their findings and techniques so that dissolution testing may be advanced to a reproducible and reliable scientific procedure.

- If labs can not be expected to agree on the results of a dissolution test, then an IVIVC obtained by one lab can not be generalized as being valid in all labs.

- Differences between dissolution results obtained in industrial labs and those obtained in agency labs raise problems in the making of regulatory decisions.

## USP Monographs for Dissolution Testing

### Table 1
Number of monographs in the US Pharmacopeia and the National Formulary which require dissolution or release tests

<table>
<thead>
<tr>
<th>Edition/year</th>
<th>Monographs for immediate-release dosage forms</th>
<th>Monographs for modified-release dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monographs</td>
<td>Extended</td>
</tr>
<tr>
<td>USP 18-NF 13/1970</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>USP 19-NF 14/1975</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>USP 20-NF 15/1980</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>USP 21-NF 16/1985</td>
<td>400</td>
<td>1</td>
</tr>
<tr>
<td>USP 22-NF 17/1990</td>
<td>462</td>
<td>18</td>
</tr>
<tr>
<td>USP 23-NF 18/1995</td>
<td>501</td>
<td>6</td>
</tr>
<tr>
<td>USP 24-NF 19/2000</td>
<td>552</td>
<td>26</td>
</tr>
<tr>
<td>USP 29-NF 24/2006</td>
<td>619</td>
<td>38</td>
</tr>
</tbody>
</table>

FDA’s Guidances for Dissolution Testing

1978 – FDA/DPA published a guideline for dissolution testing

1984 – FDA/DPA published the “Guidelines for dissolution testing: an addendum”


2010 – Guidance for Industry, The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP)

2011 – Guidance for Industry, Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions, Annex 7(R2) Dissolution Test General Chapter
# Current Official USP Dissolution Apparatuses

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Samples</th>
<th>Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus 1 (Basket)</td>
<td>Immediate-release, extended-release, and delayed-release dosage forms.</td>
<td>Temperature, rotation speed, dissolution medium</td>
</tr>
<tr>
<td>Apparatus 2 (Paddle)</td>
<td>Immediate-release, extended-release, and delayed-release dosage forms.</td>
<td>Temperature, rotation speed, dissolution medium</td>
</tr>
<tr>
<td>Apparatus 5 (Paddle over disk)</td>
<td>Primary use is for semi-solid topical dosage forms but has also been used for drug release and skin/membrane permeation for transdermal patches.</td>
<td>Temperature, rotation speed, dissolution medium</td>
</tr>
<tr>
<td>Apparatus 6 (Cylinder)</td>
<td>Transdermal system.</td>
<td>Temperature, rotation speed, dissolution medium</td>
</tr>
</tbody>
</table>

![USP Apparatus Diagrams](http://www.protechcro.com/images/01Dissolution.pdf)

Current Official USP Dissolution Apparatuses

Reciprocating Apparatus is typically used for imitating the pH changes that occur in the body and is suited for extended and sustained release dosage forms.

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Samples</th>
<th>Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus 7</td>
<td>Transdermal system, extended-release dosage forms (coated tablet)</td>
<td>Temperature, dip rate, dissolution medium</td>
</tr>
</tbody>
</table>

Current Official USP Dissolution Apparatuses

Table 1: USP 4 – flow through

<table>
<thead>
<tr>
<th>Samples</th>
<th>Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate-release, extended-release, and delayed-release dosage forms.</td>
<td>Temperature, flow rate, pulses per minute, dissolution medium</td>
</tr>
<tr>
<td>tablets, capsules, suppositories, powders, drug eluting stents, creams, gels, suspensions etc.</td>
<td></td>
</tr>
</tbody>
</table>

Does Current Dissolution Method Have Any Biological Relevance?

- Disintegration
- Solids transfer
- Dissolution
- Changing pH
- Food and drink
- Absorption
- Clearance

Picture copied from website, http://www.google.com/images?q=digest+system&hl=en&gbv=2&tbnid=isch&ei=uZQZUIT4O-ju0gHx8oCYAg&start=20&sa=N, accessed July 30, 2012

New Designs for Dissolution Testing

New Designs for Dissolution Testing

Fig. 1. Schematic illustration of the dissolution/permeation system (D/P system). Caco-2 monolayer was mounted between the apical and basal chambers. Both sides of the monolayer were filled with transport medium (apical side: pH = 6.5, volume = 8 ml, basal side: pH = 7.4, volume = 5.5 ml) and stirred by magnetic stirrers constantly. Drugs were applied to the apical side as solid, suspension, or solution.


New Designs for Dissolution Testing

- Hank’s Balanced Salts Solution (HBSS) at pH 6.8 was used as the dissolution medium, in order to accommodate the Caco-2 monolayer.
- SGF and deionized water do not support Caco-2 cell viability.
- The dissolution testing time is limited by Caco-2 cells for less than 2 hours.

Mark J. Ginski, Rajneesh Taneja, and James E. Polli, 1999, Prediction of Dissolution-Absorption Relationships from a Continuous Dissolution/Caco-2 System, *AAPS PharmSci, 1 (3) article 3*

L. Hughes et al. Dow Apparatus (FloVitro)
New Designs for Dissolution Testing

New Designs for Dissolution Testing

Fig. 7. Comparison of rescaled dissolution profile obtained from modified flow-through reservoir with in vivo data from reference (15)

New Designs for Dissolution Testing

USP4 as dissolution apparatus @ 4mL/min
150 mL SGF for 1 hour
Then, 500 SIF for 23 hours

Advantage and Disadvantage of Newly Developed Dissolution Method

Current USP Dissolution Methods
- Disintegration
- Solids transfer
- Dissolution
- Changing pH
- Food and drink
- Absorption
- Clearance
- Standardized Method

Newly Developed Dissolution Methods
Dissolution Testing: Evolving Dissolution Media for Predicting In Vivo Performance

Arzu Selen, Ph.D.
Biopharmaceutics Research Lead
Office of New Drug Quality Assessment/OPS/CDER/FDA

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012
Outline

• Background
• Dissolution test to relevance of dissolution medium
  – Recommendations from the guidance
  – Types and function
  – Some examples: product characterization, food effect, screen for alcohol dose-dumping
  – Next phase? Integration of Quality-by-Design (QbD) and Biopharmaceutics and mechanistic value
• Summary
Dissolution Rate Linked with Clinical Outcome

“IN A RECENT study of factors affecting the absorption rate and gastrointestinal irritant effect of aspirin (1) it was concluded that (a) absorption rates and incidence and severity of local irritation are interrelated, (b) both of these characteristics are a function of the dissolution rate of aspirin in its particular dosage form, and (c) there are significant differences in in vitro dissolution rates among different nationally distributed brands of aspirin tablets.”

From the Beginning

“A dissolution method (and the acceptance criteria) should be defined to deliver desired performance of a product in the intended in vivo environment.” (Ref. 2)

- IVIVC is a future objective for ER formulations
- Dissolution testing for process control, stability, minor formulation changes and manufacturing site changes. (Ref. 1)

Ref.1: Workshop co-sponsored by ASCPT/DIA/APS/FDA, 1987
Our Increasing Expectations in Drug Dissolution/Release Testing

• Provide basic criteria for drug release from the product
• For batch to batch consistency/quality (product specification)
• As potential surrogate for in vivo BE studies
• For linking the product and its in vivo performance (correlations or relationships: IVIVC or IVIVR)

- An aqueous medium- pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP)
- To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 (without enzymes)
- The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified.
- To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed (also, recommended for testing of ER products).
- A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0.
Recommendations for Dissolution Medium (Continued)

- With gelatin capsule products—medium containing enzymes (pepsin with SGF and pancreatin with SIF) may be used to dissolve pellicles.
- Use of water alone as a dissolution medium is discouraged (water source may affect test conditions such as pH and surface tension, and may change during the dissolution test - due to the influence of the active and inactive ingredients)
- For water insoluble or sparingly water soluble drug products, use of a surfactant such as sodium lauryl sulfate is recommended (Shah 1989, 1995). The need for and the amount of the surfactant should be justified.
A Short List of Dissolution Media

Standard Compendial (in USP):
• Simulated Gastric Fluid (with and without pepsin)
• Simulated Intestinal Fluid (with and without pancreatin)
• Water
• Their modifications (media with surfactants)

Additional Media (including patented “Biorelevant” media)
• Fasted-State Simulated Gastric Fluid (FaSSGF)
• Fed-State Simulated Gastric Fluid (FeSSGF)
• Fasted State Simulated Intestinal Fluid (FaSSIF)
• Fed State Simulated Intestinal Fluid (FeSSIF)
• Blank Fasted and Fed (GF) and (IF)
• And others (such as Ensure® Plus for forecasting food-effect)
Composition of FaSSGF and FeSSGF

**Fasted State Simulated Gastric Fluid (FaSSGF), pH 1.6 [30]**

<table>
<thead>
<tr>
<th>Composition</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salt (sodium taurocholate)</td>
<td>80 µM</td>
</tr>
<tr>
<td>Lecithin</td>
<td>20 µM</td>
</tr>
<tr>
<td>Pepsin</td>
<td>0.1 mg/mL</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>34.2 mM</td>
</tr>
<tr>
<td>Hydrochloric acid qs pH 1.6</td>
<td></td>
</tr>
<tr>
<td>Deionized water qs ad</td>
<td>1 L</td>
</tr>
</tbody>
</table>

**Fed State Simulated Gastric Fluid (FeSSGF), pH 5.0 [31]**

<table>
<thead>
<tr>
<th>Composition</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glacial acetic acid</td>
<td>17.12 mM</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>29.75 mM</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>237.02 mM</td>
</tr>
<tr>
<td>Deionized water qs ad</td>
<td>1 L</td>
</tr>
</tbody>
</table>

The blank medium was then mixed with UHT-milk at the ratio of 1:1

Reference: Jantratid et al., Europ. J of Pharm. and Biopharm. 69, 776-785, 2008
Last 20 - 30 years:

Dissolution/release Testing

Quality control tool

Links drug product to its in vivo performance

And recently:
- Can/should QbD merge the two paths?
- Does it help if single and/or multiple media are used?
Desired State for Drug Release/Dissolution Method

Has *in vivo* relevance

Reliable, reproducible, well characterized method

Influenced by Critical Quality Attributes

Supports linking process, product and patient
Desired State for Drug Release/Dissolution Media

- Standardized, well-characterized, easy to prepare and stable during testing
- Has *in vivo* relevance
- Facilitates Assessment of Critical Quality Attributes - has product relevance

Supports linking process, product and patient
Considerations for Selection of Dissolution Medium

- Consistent with route of drug administration and *in vivo* environment (Relevance)
- Physiological and conditional similarity (such as fed/fasted)
- Function (mechanistic understanding, exploratory vs. predictive)
- Possible alternates (such as simplified media)
- Ease of preparation (reliable method)
- Standardized (reproducible and stable during testing)
**In Vitro Tests for Product Characterization**  
(using compendial and/or non-compendial methods)

- USP Apparatus and compendial media (and/or modifications)
  - Assessing solubility, dispersion and conditions leading to precipitation
- Bile salt solubility
  - Exploring *in vivo* solubilizing capacity of gut lumen
- Formulation dispersion, dissolution and drug precipitation
  - Formulation development
  - Testing changes in formulation and product and environment interactions (food-effect, alcohol dose-dumping)
- *In vitro* digestion/lipolysis tests as possible predictors for food effect (effect of the digestion products)
Effect of Likely Components in the Gut Lumen on Rate and Extent of Dissolution

Mean Dissolution Profiles of Romazin Tablets (Troglitazone®) in Various Media

Furosemide Solubility in Simulated Gastric Media

FaSSGF (Fasted-State Simulated Gastric Fluid, pH 1.6) and FeSSGF (Fed State Simulated Gastric Fluid, pH 5), and corresponding blank buffers (without surfactant)

Reference: From the 2011 AAPS poster presentation of Sarah Gordon, Anette Muellertz and others
Exploring Food Effect and Possible Use of Simplified Biorelevant Media

Ketoconazole Release from Nizoral® Tablets in Biorelevant Media and Respective Blank Buffers

Ketoconazole Release from Nizoral® Tablets in Simplified “Biorelevant” Dissolution Media (Continued)
Single Medium vs. pH Gradient Method


Single Medium

Biorelevant pH Gradient Method

900 mL pH 6.8 Phosphate buffer
In vitro results from the biorelevant pH gradient method predict food effect

Plasma diclofenac concentrations after a single oral dose of modified-release diclofenac sodium pellets (n=16 healthy volunteers, fasted and fed states).
In Vitro Release of Opioids from Oral Prolonged-release Preparations in Simulated Gastric Fluid and Simulated Gastric Fluid with Ethanol

Screening for Alcohol Effect on Drug-Product Integrity

Correlation Between Hydromorphone Cmax and \textit{In Vitro} Release at 30 min. and 60 min

Palladone XL was given with 240 mL water and also with 4%, 20% and 40% alcoholic beverage

Reference: Lennernas, Molec. Pharma. 6(5), 1429-1440, 2009
Integration of QbD and Biopharmaceutics

Mechanistic Understanding (in vivo and in vitro)

Patient Benefit

QTPP driven specification

June 2009 workshop of QbD and Biopharmaceutics Rockville, MD
Ref.: AAPSJ, 12(3), 465-472, September 2010
Summary: Towards Developing an *In Vitro* Test Mimicking *In Vivo* Conditions (Mechanistic/Predictive Methods)

- Dissolution/release test method should be well characterized (sources of variability and the impact of changes should be known).
- Dissolution test media should be physiologically meaningful.
- Dissolution/release test conditions (e.g. agitation), duration and sample collection times should be consistent with its intended release pattern/environment, and use (as in Quality Target Product Profile).
Oral Bioperformance & 21st Century Dissolution Testing

Gregory E. Amidon
Research Professor of Pharmaceutical Sciences
College of Pharmacy
University of Michigan
“What is it that we can’t do today, but if we could, it would revolutionize our business?”

Joel Barker
Futurist

Comprehensive computational tools and meaningful in vitro test methods that accurately reflect and predict oral bioperformance would revolutionize oral formulation development.
Topics

• Where are we now?
• What opportunities are there? There are many!
  • GI physiology
    • Fluid volume
    • Hydrodynamics
    • Buffer (bicarbonate)
  • Advanced dissolution methods
    • Two phase systems (simulating dissolution and absorption)
    • Two compartment systems (simulating stomach and intestine)
  • Computational Tools
    • Fluid Dynamics
    • Dissolution
    • Absorption Modeling
USP Compendial Tests for Oral Bioperformance

- 1950: Disintegration Test
- 1970: Dissolution Apparatus 1 (rotating basket)
- 1980: Dissolution Apparatus 2 (paddle)
- .......
- .......

![Graph showing the number of pages referenced in USP for disintegration and dissolution tests over the years.]
Dissolution Testing is what links the dosage form to the proven efficacy (eg: typically the clinical lot used in the Phase 3 pivotal efficacy study)!

......

Dissolution testing is what links every lot of the dosage form from every manufacturer to the labeling (proven efficacy and safety)! This can be 100s or 1000s of lots separated by years or decades as well as continents from the pivotal efficacy lot.
Some areas of success (1970-2012)

- Dissolution Testing as an “analytical” measure of:
  - Product consistency
  - Product quality
  - Manufacturing process control
- IVIVC, IVIVR, IVIVE
- BCS
- Intestinal media simulation
  - FaSSIF
  - FeSSIF
- Physiologically relevant solubility
- Improved understanding of GI environment
- Application of computational tools
Some weaknesses (1970-2012)

- IVIVC, IVIVR, IVIVE
- Application of oral physiology understanding to drug and drug product testing
- Dissolution Testing as in vivo simulation
- Application of advanced computational tools
- Application of comprehensive physicochemical principles to oral absorption
The price of “less than ideal” in vitro methods is:

• Over-discriminatory in vitro test methods
  • Result is wasted resources and delays in the development of new products to meet unmet medical needs
    • Chasing down unimportant problems
    • Conducting unnecessary clinical or animal testing
    • Spending unnecessary development and analytical resources
    • Slowing development of innovative dosage forms for difficult to deliver drugs

• Under-discriminatory in vitro test methods
  • Result in a lack of meaningful product quality control
    • Difficulty comparing innovator and generic products
    • Product failure (eg: efficacy and/or safety) in patients!
A better dissolution test!

More Accurate Oral Bioperformance Prediction would help:

• Formulation finding/screening (early development)
• Define meaningful in vitro performance requirements such as disintegration, dissolution, supersaturation extent and time, functional excipient impact (solubilizer, precipitation inhibitor) etc.
• Optimize dosage form delivery rate
• Enhance material and process understanding (≡ Quality by Design)
• Facilitate meaningful in vitro testing of varying in vivo conditions
Topics

• Where are we now?
• What opportunities are there (there are many)?
  • GI physiology
    • Fluid volume
    • Hydrodynamics
    • Buffer (bicarbonate)
  • Advanced dissolution methods
    • Two phase systems (simulating dissolution and absorption)
    • Two compartment systems (simulating stomach and intestine)
  • BCS Advances
  • Computational Tools
    • Fluid Dynamics
    • Dissolution
    • Absorption Modeling
What have we learned about human physiology that might related to dissolution testing?

**Key considerations include:**

- Fluid volume
- Intestinal surface area
- Buffer (bicarbonate)
- pH (average, range)
- Ionic strength
- Surfactants (bile acids)
- Carbonic anhydrase
- Hydrodynamics
- Residence time
- Stomach emptying rate
- ....

**Intestinal Contents**

- Bicarbonate (mEq L\(^{-1}\))
- Bile salts (mM)
- Lipids (mg/mL)
- Phospholipids (mM)
- Pepsin (mg/mL)
- Lipase
- Potassium (mM)
- Sodium (mM)
- Chloride (mM)
- Calcium (mM)
- Buffer capacity (mmol L\(^{-1}\) pH\(^{-1}\))
- Osmolality (mOsm kg\(^{-1}\))
- Surface tension (mN m\(^{-1}\))
- Viscosity
- Volume
- Shear
- pH
Physiology: What volume of liquid is the dosage form exposed to?

- Average aqueous volume in the fasted small intestine is ~100 ml (Refs: multiple)

<table>
<thead>
<tr>
<th></th>
<th>Total volume in the small intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted Mean</td>
<td>86, 81, 112±27, 109±36, 165±22, 105±72</td>
</tr>
<tr>
<td>Fasted Range</td>
<td>34-46, 37-130, 45-319</td>
</tr>
<tr>
<td>Fed Mean</td>
<td>47, 381, 590±73, 54±41</td>
</tr>
<tr>
<td>Fed Range</td>
<td>18-78, 343-491, 20-156</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>Fasted</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of liquid pockets Mean</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Number of liquid pockets Individual (approx.)</td>
<td>2, 3, 4, 5, 8</td>
<td>2, 5, 6, 7, 11</td>
</tr>
<tr>
<td>Volume of liquid pocket (mL) Median</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Physiology is complex

So - compendial dissolution testing in 900 mL with a paddle (or rotating basket) doesn’t really capture it.
Some physiological dissolution “systems”

- Artificial Dynamic GI System, TIM-1 (TNO)
- Stress test apparatus
- Dissolution/Permeation system (uses Caco-2 cells)
- Two-compartment apparatus:
  - Artificial Stomach and Duodenum (ASD)
  - FloVitro Technology (Rohm and Haas)
- Two-phase dissolution apparatus
  - Simultaneous dissolution and partitioning in single compartment containing two phases (water:organic)
In-vivo Intestinal Fluid Flow Rates

Hydrodynamics of dissolution apparatus: USP Apparatus 2 - Velocity & Shear Profiles

- Highest velocities occur at the tip of the paddle (~20 cm/sec)
- The lowest velocities are directly beneath the centerline of the impeller and around the shaft of the impeller.

- The Reynold’s numbers (Re) vary depending on the rotational speed and location (Re ~ 10^4).
- The shear rates throughout the vessel are heterogeneous.
  
  Maximum shear rates: 92s^{-1} at 50 RPM
  Average shear rates: ~ 20s^{-1} at 50 RPM

Flow Through Cell

- May allow for testing at more physiologically relevant Reynolds number (5 – 300) and flow rates (0.1 – 0.6 cm/sec).

Impact of Fluid Shear on Particle Dissolution ($h_{\text{app}}$): High Performance Computational Analysis

(2) Wang, Brasseur, Penn State University (unpublished)
Importance of physical chemistry and physiologic buffer (bicarbonate)

- **Drug Properties:**
  - Solubility
  - pKa
  - Diffusion coefficient
  - Particle size

- **Physiological Properties:**
  - pH
  - Buffer species and concentration
  - Fluid hydrodynamics
  - Intestinal motility
  - Bulk concentration
  - Volume and temperature etc.
Bicarbonate Buffer Physiological Relevance

• Bicarbonate is secreted by the pancreas and epithelial cells throughout the GI lumen.

\[ \text{GI Lumen} \]

\[ CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \]

[Chemical reactions]

Dissolution (37°C) of Ibuprofen in bicarbonate buffer compared to phosphate buffer (rotating disk)

Dissolution in 50 mM phosphate buffer @ pH=7.2 (USP test) is 0.7 mg/cm²/min
Topics

• Where are we now?
• What opportunities are there (there are many)?
  • GI physiology
    • Fluid volume
    • Hydrodynamics
    • Buffer (bicarbonate)
  • Advanced dissolution methods
    • Two phase systems (simulating dissolution and absorption)
    • Two compartment systems (simulating stomach and intestine)
• BCS Advances
• Computational Tools
  • Fluid Dynamics
  • Dissolution
  • Absorption Modeling
Combining dissolution and absorption (two phase model)

- Ten + systems described in literature
- Being used in industry
- Overcome difficulties in maintaining sink conditions for poorly-soluble drugs (BCS 2, 4), super-saturable systems, and controlled-release
- Circumvent analytical difficulties associated with lipid-based capsule formulations
- Simultaneously study impact of formulation changes (e.g. surfactants) on dissolution and absorption processes!
- Can potentially be scaled to more accurately reflect in vivo conditions!
Two-phase IVIVR: Nifedipine GITS tablets

- BCS IIc
- Sol. FaSSIF = 0.024mg/ml
- Log P = 2 - 4
Two phase physiologic dissolution model

\[ P_m = 5 \times 10^{-4} \text{ cm/sec}, \text{ particle radius} = 50 \mu\text{m} \]

**BCS Class II**

Sol = 100µg/mL Dose = 25 mg

(Dose number = 1)

A/V = 2.3

Vw = 100 mL
Two phase physiologic dissolution model
\[ P_m = 2 \times 10^{-4} \text{ cm/sec}, \text{ particle radius} = 50 \, \mu\text{m} \]

BCS Class II
Sol=100µg/mL Dose = 25 mg
(Dose number = 1)
A/V = 2.3
Vw = 100 mL
Two phase physiologic dissolution model
\[ P_m = 1 \times 10^{-4} \text{ cm/sec}, \ \text{particle radius} = 50 \ \mu\text{m} \]

BCS Class II
Sol = 100 \mu g/mL Dose = 25 mg
(Dose number = 1)
A/V = 2.3
Vw = 100 mL
Two phase physiologic dissolution model

$P_m = 1 \times 10^{-4} \text{ cm/sec}$, particle radius = 5 µm

BCS Class II

Sol = 100 µg/mL
Dose = 25 mg
(Dose number = 1)
A/V = 2.3
Vw = 100 mL
Stomach and intestine: Two-compartment dissolution apparatus

- Several publications in literature describing Artificial Stomach-Duodenum (ASD)
- Used in pharmaceutical industry
- Used to compare ASD performance with *in vivo* bioavailability values

Relative bioavailability estimation of carbamazepine crystal forms

## Impact of stomach pH on Oral Absorption of Anticancer Agents

### Table 3 Effect of acid-reducing agents on the oral absorption of targeted anticancer agents

<table>
<thead>
<tr>
<th>Drug (dose)</th>
<th>Acid-reducing agent</th>
<th>Mean change</th>
<th>Subjects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib (50 mg)</td>
<td>Famotidine (40 mg) 10 hours prior to dasatinib</td>
<td>↓ 61%</td>
<td>Healthy subjects</td>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Famotidine (40 mg) 2 hours after dasatinib</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>Dasatinib (50 mg)</td>
<td>Maalox 30 ml 2 hours prior to dasatinib</td>
<td>←</td>
<td>Healthy subjects</td>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Maalox 30 ml coadministered with dasatinib</td>
<td>↓ 55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (100 mg)</td>
<td>Omeprazole (40 mg) daily for 5 days and on day 5 with dasatinib</td>
<td>↓ 43%</td>
<td>Healthy subjects</td>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
</tr>
<tr>
<td>Erlotinib (150 mg)</td>
<td>Omeprazole (40 mg) daily for 7 days</td>
<td>↓ 46%</td>
<td>Healthy subjects</td>
<td>Primary metabolite&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Erlotinib (150 mg)</td>
<td>Ranitidine 300 mg daily for 5 days and erlotinib 150 mg single dose 2 hours after ranitidine dose on third day</td>
<td>↓ 33%</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Erlotinib (150 mg)</td>
<td>Ranitidine 150 mg b.i.d. for 5 days and erlotinib 150 mg single dose 2 hours before and 10 hours after ranitidine on third day</td>
<td>↓ 15%</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Gefitinib (250 mg)</td>
<td>Two oral doses of 450 mg ranitidine (13 hours and 1 hour before 250 mg of gefitinib) followed by sodium bicarbonate to maintain gastric pH above 5 for 8 hours</td>
<td>↓ 44%</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Imatinib (400 mg)</td>
<td>Omeprazole (40 mg) daily for 5 days and on day 5 with imatinib</td>
<td>←</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Imatinib (400 mg)</td>
<td>Maalox Max (20 ml) 15 minutes before imatinib</td>
<td>←</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Lapatinib (1,250 mg)</td>
<td>Esomeprazole (40 mg) daily for 7 days at bedtime</td>
<td>↓ 26%</td>
<td>Cancer patients</td>
<td>NA</td>
</tr>
<tr>
<td>Nilotinib (400 mg)</td>
<td>Esomeprazole (40 mg) daily for 6 days and on day 6 with nilotinib</td>
<td>↓ 34%</td>
<td>Healthy subjects</td>
<td></td>
</tr>
<tr>
<td>Axitinib (5 mg)</td>
<td>Rabeprazole (20 mg) q.d.</td>
<td>↓ 15%</td>
<td>Cancer patients</td>
<td></td>
</tr>
</tbody>
</table>

AUC, area under the curve; <i>C<sub>max</sub></i>, peak plasma concentration; NA, not applicable.

<sup>a</sup>Primary metabolite data.

Advantages & disadvantages of two-compartment systems

**Advantages**
- Sequentially exposes drug to gastric followed by intestinal media
  - Differing media properties in stomach and intestine (e.g. pH, lipid & bile salt concentrations) can affect dissolution
- Captures *in vivo* gastric-emptying rates and flow rates
  - Can vary to simulate effect on dissolution
- Potential to integrate peristaltic motion

**Disadvantages**
- Does not contain separate phase/chamber for absorption
  - Assumes dissolved drug proportional to drug in plasma
Topics

• Where are we now?
• What opportunities are there (there are many)?
  • GI physiology
    • Fluid volume
    • Hydrodynamics
    • Buffer (bicarbonate)
  • Advanced dissolution methods
    • Two phase systems (simulating dissolution and absorption)
    • Two compartment systems (simulating stomach and intestine)
• Computational Tools
  • Fluid Dynamics
  • Dissolution
  • Absorption Modeling
Exciting research is going on….

Motility and Absorption in the Small Intestine
Quantification of Small Bowel Water/Physiology
Coupling Biorelevant Dissolution Testing with PBPK Modeling
Modeling Hydrodynamics in the Intestine
Bicarbonate Buffer and Surface pH
In Vitro Dynamic Lipolysis Model
Precipitation Kinetics of Poorly Soluble Drugs under Supersaturated State and Precipitation Inhibitors
Rotating Disk as a Dissolution Tool
Artificial Stomach Duodenum (2 compartment dissolution)
Miniscale Dissolution-membrane Partitioning System
Two Phase Dissolution System
Two Compartment Caco2 model /Mini-scale Dissolution

In vivo and computational biopharmaceutical aspects of precipitation and intestinal permeability
Dynamic Dissolution (TIM-1)
Methods for Estimation of Biorelevant Drug Solubility
Combining Experimental and Computational Approaches for Predicting Oral Bioperformance
Future Direction and Research Needs

- Enhanced Understanding In Vivo environment (human, animal)
  - Hydrodynamics
  - Volume
  - Gastric Emptying
  - Fluid content, buffer
- Development of Relevant In Vitro Methodologies
  - Likely not one-size-fits-all
  - Address/simulate dissolution and absorption kinetics
  - Precipitation assessment / inhibition
  - Modified / Delayed Release optimization
  - Development of Advanced Computational Tools (In Vitro & In Vivo)
    - Hydrodynamics
    - Dissolution
    - Absorption
    - Metabolism
- Application of physicochemical principles to dissolution
Questions/discussion
Dissolution Testing and Quality-by-Design

Lawrence X. Yu, Ph. D.
Deputy Director for Science and Chemistry
Office of Generic Drugs
Food and Drug Administration

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012
Quality-by-Design

• ICH Q8(R2)
  – Pharmaceutical Quality-by-Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

• Quality-by-Design Tools
  – Prior knowledge
  – Risk assessment
  – Design of experiments and data analysis
  – Process analytical technology (PAT) tools
QbD: Linking Process/Product/Patient

- Patient
- Product
- Process

Quality Target Product Profile
Critical Quality Attributes
Material Attributes & Process Parameters
Quality Target Product Profile (QTPP)

- QTPP
  - A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality (performance)

- Guide to establish product design strategy and keep product development effort focused and efficient
What Does QTPP Include?

• Intended use in clinical setting
  – Route of administration, dosage form (delivery systems), and container closure system

• Quality attributes of drug product
  – Appearance, Identity, Strength, Assay, Uniformity, Purity/Impurity, Stability, and others

• Active pharmaceutical ingredient release or delivery and attributes affecting pharmacokinetic characteristics (safety and efficacy)
  – Dissolution, aerodynamic performance, etc.
Dissolution and QbD

• Dissolution can be used to help relate the “Product” to the “Patient” in the QbD paradigm
  – Relate *in vivo* performance of a drug to *in vitro* measurements
  – Enable development of clinically relevant specifications
  – Understand the impact of formulation and manufacturing process variations

• Clinically meaningful dissolution specifications that assure consistent therapeutic benefit can aid manufacturing control strategy development
Roles of Dissolution Testing

• A quality control tool
  – Batch-to-batch consistency
  – Provide quality assurance

• An *in vitro* surrogate for product performance
  – Formulation development
  – Bioequivalence studies
Dissolution for Quality Control

• A product specific quality control test
  – The hydrodynamics and medium for this test are chosen for reproducibility and detection of product changes
  – The design of this test is not constrained by a desire to mimic in vivo conditions
  – Acceptance criteria for consistency of batches
Dissolution for *In Vivo* Performance

- A biorelevant dissolution test
  - Correlates with *in vivo* dissolution
    - The hydrodynamics and medium for this test are chosen to reflect *in vivo*
    - Biorelevant dissolution test is a one-time test to provide a baseline for product performance
Predictive Dissolution Enables Efficient Product Development

• It is unrealistic to conduct *in vivo* bioequivalence studies for every formulation and manufacturing change during pharmaceutical development or for every post-approval change.

• Predictive dissolution can streamline product development and lead to time and cost savings during product development while enhancing the significance of *in vitro* testing.
FDA IVIVC Guidance

• IVIVC = in vitro-in vivo correlation

• Contents
  – Data/formulation requirements
  – Predictability evaluation
  – Application in waivers of in vivo bioequivalence studies and dissolution specifications (pre- and post-approval)
Oral Drug Absorption Process

- Gastric Emptying
- Disintegration Dissolution
- Transit
- Dissolution
- Permeation
- Metabolism
Limits to Oral Drug Absorption

- Gastric emptying
- Dissolution
  - DS dissolution rate = \( D \cdot S/h \cdot (C_s - C_l) \)
    - \( D \) - diffusion coefficient
    - \( S \) - dissolution surface area: Drug substance
    - \( h \) - Aqueous boundary thickness
    - \( C_s \) - Solubility: Drug substance
    - \( C_l \) - Concentration in dissolution media
- Permeability: Drug substance
In Vitro and In Vivo Relationship

- Limits to oral drug absorption
  - Dissolution-limited
  - Solubility-limited
  - Permeability-limited

\[
\frac{dM}{dt} = \frac{D}{h} S (C_s - C)
\]
The CAT Model

Small Intestinal Tract

\[ \frac{\text{d} M_{nl}}{\text{d} t} = K_z M_{nl} - K_t M_{nl} - \frac{3D M_{nl}}{\rho h r} (C_2 - \frac{M_{nl}}{V_n}), n = 1, 2, ..., 7 \]

\[ \frac{\text{d} M_{nl}}{\text{d} t} = K_z M_{nl} - K_t M_{nl} - \frac{2P_{drf} M_{nl}}{R} + \frac{3D M_{nl}}{\rho h r} (C_2 - \frac{M_{nl}}{V_n}), n = 1, 2, ..., 7 \]

\[ \frac{\text{d} M_0}{\text{d} t} = K_a \sum_{n=1}^{7} M_{nl} F = F_0 \cdot F_h = F_h M_a / M_0 = \frac{F_h}{M_0} \int_{t=0}^{\infty} K_a \sum M_n \text{d}t \]
Predicting Oral Absorption

- Human Permeability (cm/hr) vs. Fraction of Dose Absorbed
  - Predicted
  - Experimental

- Particle Diameter (μm) vs. Fraction of Dose Absorbed
  - Dissolution-limited
  - Permeability-limited
  - Solubility-limited

- Dose vs. Fraction of Dose Absorbed
  - Dose = 250 mg
  - Dose = 500 mg
  - Dose = 1000 mg
The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability.

- The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability.

<table>
<thead>
<tr>
<th>Biopharm. Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

- The understanding of drugs based on BCS can aid in formulation and manufacturing development in a QbD paradigm.
BCS Class I and III Drugs

Rapid dissolution for BCS Class I drugs and very rapid dissolution for BCS Class III drugs ensure that in vivo dissolution is not the rate limiting step. Bioequivalence is assured provided no effect of excipient on absorption and similar dissolution profiles.
IVIVR possible for BCS Class II drugs and difficult for BCS Class IV drugs. In reality, it is often not attempted to develop *in vitro* dissolution that is predictive of in vivo.
BCS Class I

- BCS Class I drugs formulated in an immediate release dosage forms
  - No bioequivalence studies may be needed for developing “predictive” dissolution
  - Rapid dissolution may be used for formulation development and establishment of design space
  - Rapid dissolution for BCS Class I drugs in immediate release dosage forms may be used to justify formulation and manufacturing changes
BCS Class II

- BCS Class III drugs formulated in an immediate release dosage forms
  - No bioequivalence studies may be needed
  - Very rapid dissolution may be used for formulation development and establishment of design space
  - Very rapid dissolution for BCS Class III drugs in immediate release dosage forms may be used to justify manufacturing changes
  - Excipient effect needs to be further investigated
BCS Class II and IV

- BCS Class II and IV drugs formulated in an immediate release dosage forms
  - Bioequivalence studies are most likely needed to develop predictive dissolution
  - Predictability of biorelevant dissolution should be further explored and investigated
Extended-release Dosage Forms

• Extended-release Dosage Forms
  – Bioequivalence studies are likely needed to establish IVIVC/IVIVR and develop predictive dissolution
  – Predictive dissolution can then be used to support establishment of a design space
  – IVIVC/IVIVR can be used to support manufacturing changes
Dissolution for a BCS Class I Drugs

![Graph showing the dissolution profile of different ANDA formulations and UMAB counterparts over time in minutes, with various markers and colors representing different formulations.](chart.png)
In Vitro vs. In Vivo Dissolution

IR suspension

A

% Dissolved

0 0.2 0.4 0.6 0.8 1 1.2

Time (hr)

in vivo.fasted
in vivo.fed
in vitro (water)

IR tablet

B

% Dissolved

0 1 2 3 4 5 6

Time (hr)

in vivo.fasted
in vivo.fed
in vitro (1% SLS)
in vitro (0.1% SLS)

XR tablet

C

% Dissolved

0 5 10 15 20 25 30

Time (hr)

in vivo.fasted
in vivo.fed
Weibull input
in vitro (water)

XR capsule

D

% Dissolved

0 10 20 30 40 50

Time (hr)

in vivo.fasted
in vivo.fed
Weibull input
in vitro (0.1% SLS, 50rpm)
in vitro (0.1% SLS, 75rpm)
Future Directions

• Application of the QbD approach has the potential to bridge the gaps between in vitro measurements and *in vivo* performance
  – A science based approach incorporating studies both in the laboratory and clinic
  – Utilization of advanced dissolution methodologies for predictive dissolution

• Other approaches other than IVIVC/IVIVR are possible that provide increased product and process understanding
Conclusions

• There are many tools related to dissolution that can aid in implementation of QbD
  – Biorelevant dissolution methods, which may utilized advanced apparatus and/or media
  – Predictive dissolution modeling
  – IVIVC or IVIVR studies

• All of these tools can aid product quality
  – Enhanced product and process understanding
  – Clinically relevant specifications