Drug Absorption and Bioavailability

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National Institutes of Health
Clinical Center
GOALS of Drug Absorption and Bioavailability Lecture

• Factors Affecting Drug Absorption
• Estimation of Bioavailability
• Clinical Significance of Differences in Bioavailability
• Prediction of Bioavailability in High-Throughput Drug Candidate Screening
Factors Affecting DRUG ABSORPTION

- **Biopharmaceutic Factors**
  - Tablet compression
  - Coating and Matrix
  - Excipients

- **Interactions**
  - Food
  - Other Drugs
  - Bacteria

- **Physiological Factors**
Change in PHENYTOIN Excipients Results in Epidemic Toxicity*

Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
- INTERACTIONS
  - Food
  - Other Drugs
  - Bacteria
- Physiologic Factors
ENTERIC METABOLISM OF DIGOXIN*

Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
- Interactions
- PHYSIOLOGICAL FACTORS
Drug Absorption

Passive Non-Ionic Diffusion:

Primary mechanism for most drugs.
Drug Absorption

- Specialized Transport Mechanisms

Large Neutral Amino Acid Transporter:

*L-Dopa, Methyldopa, Baclofen*
Drug Absorption

- Specialized Transport Mechanisms

Oligopeptide Transporter (PEPT-1):

Amino-beta-lactams

ACE Inhibitors
Drug Absorption

- Specialized Transport Mechanisms

Monocarboxylic Acid Transporter:

*Salicylic acid*

*Pravastatin*
FALLACIES Concerning Gastric Drug Absorption

• Weakly Acidic Drugs absorbed only in the stomach (pH partition hypothesis)

• Weakly Basic Drugs absorbed in the small intestine (pH partition hypothesis)

• Gastric pH is always acidic

**In Fact, most drug absorption occurs in the SMALL INTESTINE**
# ASPIRIN ABSORPTION FROM STOMACH AND SMALL INTESTINE


## TABLE 1: ASPIRIN (ASA) ABSORPTION FROM SIMULTANEOUSLY PERFUSED STOMACH AND SMALL INTESTINE (3)

<table>
<thead>
<tr>
<th>pH</th>
<th>ASA ABSORPTION (micromol/100 mg protein/hr)</th>
<th>ASA SERUM LEVEL (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STOMACH</td>
<td>SMALL BOWEL</td>
</tr>
<tr>
<td>3.5</td>
<td>346</td>
<td>469</td>
</tr>
<tr>
<td>6.5</td>
<td>0</td>
<td>424</td>
</tr>
</tbody>
</table>
Variation in Gastric and Intestinal pH*

PHYSIOLOGICAL FACTORS Affecting Drug Absorption

- **Rate of gastric emptying** is a major determinant of *initial delay* in drug absorption.

- **Intestinal motility** is a determinant of the *extent* of drug absorption.
PATTERNS OF GASTRIC MOTOR ACTIVITY

FASTING \((Cyclical\ Pattern < 2\ HR)\)

- Phase 1 - Quiescence
- Phase 2 - Irregular Contractions
- Phase 3 - Major Motor Complex Burst
- Phase 4 - Transition Period
Interdigestive Intestinal Motor Activity in Humans*

PATTERNS OF GASTRIC MOTOR ACTIVITY

POST PRANDIAL (Up to 10 hr delay)

- Pylorus constricted
- Antral contractions reduce particle size
GI TRANSIT - SUSTAINED-RELEASE CARBAMAZEPINE FORMULATION*

EXTENT RELEASED

Subject 5
75%  56%

Subject 6
75%  56%

Variation in “Peak” Levels

**ACETAMINOPHEN**

Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*

Factors Affecting RATE and EXTENT of Drug Absorption

Drug Tablet or Capsule

Stomach
- Gastric Emptying Time
- Acid Hydrolysis

Drug in Solution

Disintegration

Drug in Small Particles

Dissolution

Heart

Somatic Circulation
- Muscle, Fat, Etc.

Liver
- 1st-Pass Metabolism

Portal Vein

Splanchnic Circulation
- Splanchnic Blood Flow

Site of Maximal Absorption

Reserve Length

Absorption Complete

Small Intestine
- Transit Time
- Imprisonal Surface Transporters
- 1st-Pass Metabolism

Colon
- Transit Time
- Bacterial Metabolism
**RESERVE LENGTH**

*RESERVE LENGTH* is the anatomical length over which absorption of a drug *can* occur *MINUS* the length at which absorption is complete.
Effect of METOCLOPRAMIDE on \textbf{Digoxin} Absorption*

Effect of PROPANTHELINE on Digoxin Absorption*

Factors Affecting RATE and EXTENT of Drug Absorption

- Drug Tablet or Capsule
- Stomach
  - Gastric Emptying Time
  - Acid Hydrolysis
- Drug in Solution
- Disintegration
- Drug in Small Particles
- Dissolution
- Portal Vein
- Small Intestine
  - Mucosal Surface
  - First-Pass Metabolism
  - Transit Time
  - Bacterial Metabolism
- Liver
  - First-Pass Metabolism
- Splanchnic Circulation
  - Splanchnic Blood Flow
- Somatic Circulation
  - Muscle, Fat, Etc.
- Heart
  - Reserve Length
  - Absorption Complete
Normal Intestinal Villi
Broad Intestinal Villi in a Patient with SPRUE
Digoxin Levels in Patients with INTESTINAL MALABSORPTION*

<table>
<thead>
<tr>
<th>DOSE FOR BOTH GROUPS = 0.25 mg/day.</th>
<th>CONTROLS</th>
<th>MALABSORPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>[DIGOXIN] (ng/mL)</td>
<td>1.3 ± 0.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>URINE D-XYLOSE EXCRETION (gm/5 hr)</td>
<td>5 – 8†</td>
<td>1.1 – 4.1</td>
</tr>
</tbody>
</table>

† NORMAL RANGE

Factors Affecting RATE and EXTENT of Drug Absorption
P-GLYCOPROTEIN EFFLUX PUMP

INTESTINAL LUMEN

OUT

MEMBRANE

IN

SLIDE COURTESY OF M. GOTTESMAN
## Bioavailability of Some P-Glycoprotein Substrates

### > 70% Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>100</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>99</td>
</tr>
<tr>
<td>Methadone</td>
<td>92</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>82</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>77</td>
</tr>
</tbody>
</table>

### 30% - 70% Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>70</td>
</tr>
<tr>
<td>Indinavir</td>
<td>65</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>60</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>55</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>55</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>48</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>38</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>35</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>32</td>
</tr>
</tbody>
</table>

### < 30% Absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>F %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>28</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>25</td>
</tr>
<tr>
<td>Morphine</td>
<td>24</td>
</tr>
<tr>
<td>Verapamil</td>
<td>22</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>18</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>15</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>13</td>
</tr>
<tr>
<td>Torvastatin</td>
<td>12</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>5</td>
</tr>
</tbody>
</table>
> 70% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

SYSTEMIC CIRCULATION

GUT WALL

SMALL BOWEL

75% NET ABSORPTION

50%

25%

P-gp

100%

50%

25%

25% UNABSORBED

EFFECTIVE ABSORBING SURFACE
FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION
Sites of **FIRST-PASS** Elimination

- **INTESTINAL MUCOSA**
  - CYP Enzymes
  - P-Glycoprotein
- **LIVER**
  - CYP Enzymes
FIRST-PASS METABOLISM
# First-Pass Metabolism

**P-Glycoprotein Transport**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDOSTERONE</td>
<td>MORPHINE*</td>
</tr>
<tr>
<td>CYCLOSPORINE*</td>
<td>NORTRIPTYLINE</td>
</tr>
<tr>
<td>ISOPROTERENOL</td>
<td>ORGANIC NITRATES</td>
</tr>
<tr>
<td>LIDOCAINE</td>
<td>PROPRANOLOL</td>
</tr>
</tbody>
</table>

* Known P-Glycoprotein Substrates
Factors Affecting **RATE** and **EXTENT** of Drug Absorption
GOALS of Drug Absorption and Bioavailability Lecture

• Factors Affecting Drug Absorption

• ESTIMATION OF BIOAVAILABILITY

• Clinical Significance of Differences in Bioavailability

• Prediction of Bioavailability
BIOAVAILABILITY is the RELATIVE AMOUNT \((F)\) of a drug dose that reaches the systemic circulation unchanged and the RATE at which this occurs.
Serum Concentration-Time Curve after a Single Oral Dose
Significance of AUC

\[ dE = CL_E \cdot C \, dt \]

\[ E = CL_E \int_0^\infty C \, dt \]

\[ D \cdot F = CL_E \cdot \text{AUC} \]
Calculation of AUC
Trapezoidal Rule

From: Rowland M, Tozer TN. Clinical Pharmacokinetics. p 470.
AUC A > B

BUT IS A BETTER THAN B?
**ABSOLUTE Bioavailability**

\[
\% \text{ Absorption} = \frac{D \text{ IV} \cdot AUC \text{ oral}}{D \text{ oral} \cdot AUC \text{ IV}} \times 100
\]

Comparison here is between an ORAL and an IV Formulation.
**RELATIVE Bioavailability**

\[
\% \text{ Relative B.A.} = \frac{D_{\text{Ref.}} \cdot AUC_{\text{Test}}}{D_{\text{Test}} \cdot AUC_{\text{Ref.}}} \times 100
\]

Comparison here is between 2 ORAL Formulations
**How to keep salicylate blood levels up**

Mean salicylate plasma levels measured in 25 patients for 6 hours following ingestion of 2 Timed-Release aspirin tablets vs. those achieved during a four-hour period following two 5-grain aspirin tablets:

- **Timed-Release aspirin, 20 grains (2 tablets, 10 grains each)**
- **Regular aspirin, 10 grains (2 tablets, 5 grains each)**

**...even when your arthritis patient isn’t.**

A shift at bedtime from Bayer 5-grain Aspirin to Bayer Timed-Release Aspirin can help maintain the persistent serum salicylate levels so important for control of arthritis inflammation and pain—without the need to interrupt sleep.

Formulated especially for use in arthritis, this extended-release dosage form provides 10 grains (650 mg) of microencapsulated aspirin in each tablet. While patients sleep, aspirin is released systematically into the bloodstream. Salicylate levels and anti-inflammatory activity are prolonged and patients should experience less nighttime awakening due to pain and some relief of discouraging morning stiffness.

So during the day, when arthritis patients are up to take medication on schedule, recommend Bayer 5-grain Aspirin. But during the sleeping hours, for extended analgesic and anti-inflammatory activity, recommend Bayer Timed-Release Aspirin, 2 tablets, 10 grains each. It provides all the advantages of aspirin—throughout the night.

**Bayer Timed-Release Aspirin**
**RELATIVE** Bioavailability

\[
\% \text{ Relative B.A.} = \frac{D_{\text{Ref.}} \cdot AUC_{\text{Test}}}{D_{\text{Test}} \cdot AUC_{\text{Ref.}}} \times 100
\]

AUC Values have to be normalized for dose.

*Normalized for Dose*
ASSESSMENT of Bioavailability

• AUC Estimates can be used to estimate Extent of Drug Absorption

• **Recovery of Parent Drug in Urine can be used to estimate Extent of Drug Absorption**

• How is ABSORPTION RATE assessed?
  - \( T_{\text{MAX}} \)
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.
Extent of Absorption from Renal Excretion of Unchanged Drug

Since: \( F \cdot D = E \) and \( E = \left( \frac{CL_E}{CL_R} \right) E_R \)

\[
F \cdot D_{\text{oral}} = \left( \frac{CL_E}{CL_R} \right) E_{R(\text{oral})} \quad \text{and} \quad D_{IV} = \left( \frac{CL_E}{CL_R} \right) E_{R(IV)}
\]

So: \( \% \text{ Absorption} = \frac{D_{IV} \cdot E_{R(\text{oral})}}{D_{\text{oral}} \cdot E_{R(IV)}} \times 100 \)
ASSESSMENT OF Bioavailability

• AUC Estimates Can Be Used to Estimate Extent of Drug Absorption.

• Recovery of Parent Drug in Urine Can Be Used to Estimate Extent of Drug Absorption.

• HOW IS ABSORPTION RATE ASSESSED?
  - T_{\text{MAX}}
  - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.
INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES

\[ \text{ABSORPTION FUNCTION} \quad G(t) \quad \ast \quad H(t) \quad = \quad X(t) \]

IV DOSE

ORAL DOSE

G(t) * H(t) = X(t)
MODEL Used to Analyze Kinetics of Drug Absorption

$K_a$ is absorption rate

$K_o$ is rate of nonabsorptive loss
Calculation of **Bioavailability** from First-Order Absorption Model

\[ F = \frac{k^a}{k^a + k^o} \]
Methods for Assessment of **ABSOLUTE BIOAVAILABILITY**

- **CONVENTIONAL:**
  - IV and ORAL doses given on two separate occasions.
  - Requires two study sessions
  - Requires two sets of blood samples
  - Assumes no change in disposition parameters between studies

- **STABLE ISOTOPE:**
  - One study and set of blood samples
  - Special synthesis requirements
  - Mass Spectrometer Assay required
NAPA-\textsuperscript{\textit{13}}C\textsubscript{2}
Simultaneous Administration of Oral NAPA and IV NAPA-C\textsuperscript{13*}

MODEL Used to Analyze Oral NAPA and IV NAPA-C¹³ Kinetics*

BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

<table>
<thead>
<tr>
<th>PATIENT NUMBER</th>
<th>KINETIC ANALYSIS (%)</th>
<th>NAPA RECOVERY IN URINE* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66.1</td>
<td>65.9</td>
</tr>
<tr>
<td>2</td>
<td>92.1</td>
<td>92.1</td>
</tr>
<tr>
<td>3</td>
<td>68.1</td>
<td>69.9</td>
</tr>
<tr>
<td>4</td>
<td>88.2</td>
<td>73.1</td>
</tr>
<tr>
<td>5</td>
<td>75.7</td>
<td>75.6</td>
</tr>
</tbody>
</table>

* Corrected for absorption lag time.
Factors Affecting RATE and EXTENT of Drug Absorption
NAPA PK Model After IV Dose

\[ \text{Dose} \]

\[ V_C \quad \text{IV SPACE} \]

\[ CL_E \]

\[ CL_F = Q_F (1 - e^{PF/Q_F}) \]

\[ CL_S = Q_S (1 - e^{PS/Q_S}) \]

\[ V_F \quad \text{SPLANCHNIC} \]

\[ CL_F \text{ PARTLY REFLECTS SPLANCHNIC BLOOD FLOW} \]

\[ V_S \quad \text{SOMATIC} \]
Relationship Between $\text{CL}_F$ and Extent of NAPA Absorption*


$R^2 = 0.8, p = 0.045$
THOUGHTS About Absolute Bioavailability Studies

• Absolute Bioavailability is usually studied in Healthy Subjects, NOT in the Patient Population for whom the drug is intended.

• The Stable Isotope Method is ideally suited for studies in Special Populations (e.g. Pediatrics, Pregnant Women, other)
GOALS of Drug Absorption and Bioavailability Lecture

• Factors Affecting Drug Absorption
• Estimation of Bioavailability
• Clinical Significance of Differences in Bioavailability
• Prediction of Bioavailability
**RELATIVE Bioavailability Terms**

**Bioequivalence:** AUC and Cmax within 80% - 125% of reference compound.

**Bioinequivalence:** Greater difference in bioavailability.

**Therapeutic Equivalence:** Similar clinical effectiveness and safety.

**Therapeutic Inequivalence:** Important clinical difference in bioavailability.
AUC A > B: Therapeutic Significance?
AUC A > B: B Ineffective
AUC A > B: A and B Equally Effective
Equal AUC but Different $K_a$: B is Ineffective
Equal AUC but Different $K_a$: A is Toxic
RELATIVE BIOAVAILABILITY

CONCLUSIONS

• BIOEQUIVALENCE = THERAPEUTIC EQUIVALENCE

• BIOINEQUIVALENCE \textit{NOT NECESSARILY} = THERAPEUTIC INEQUIVALENCE
GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- Estimation of Bioavailability
- Clinical Significance
- *PREDICTION of Bioavailability* as part of *High-Throughput Drug Candidate Screening*
WHY DRUG DEVELOPMENT FAILS

• Unsuitable **Biopharmaceutical** Properties

• Unsuitable **Clinical Pharmacokinetics**

• Pharmacology (PD) **Doesn’t Work in Humans**

• **Unexpected Toxicity** is Encountered

* Ronald E. White, Bristol-Myers Squibb (From Good Ligands to Good Drugs, AAPS-NIGMS Symposium, February 19-21, 1998)
**BIOPHARMACEUTIC DRUG CLASSIFICATION**

**CLASS I:**
High Solubility - High Permeability

**CLASS II:**
Low Solubility - High Permeability

**CLASS III:**
High Solubility - Low Permeability

**CLASS IV:**
Low Solubility - Low Permeability

Three CRITICAL Biopharmaceutical Properties

• Drug **Solubility** Relative to Dose
  GOOD = Highest Dose in 250 mL H₂O, pH 1.0-7.5

• **Dissolution Rate** of Formulation
  GOOD = 85% Dissolution in 15 min

• Intestinal **Permeability** of Drugs
CORRELATION of Rates of Drug DISSOLUTION and Oral ABSORPTION

![Graph showing correlation between % Absorption and % Dissolution. The equation of the line is y = -8.6 + 1.07x and R^2 = 0.970.]

Three CRITICAL Biopharmaceutical Properties

- Drug Solubility *Relative* to Dose
- Dissolution Rate of Formulation
- *INTESTINAL PERMEABILITY* of Drug
Bioavailability vs. Jejeunal Permeability*

Bioavailability vs. *Caco-2 Cell Permeability* $P_{app}$

Evaluation of Caco-2 Cell Model

• ADVANTAGES
  - *In Vitro* Method
  - Suitable for High-Throughput

• DISADVANTAGES
  - ↓ Paracellular Permeability
  - ↓ Drug Metabolizing Enzymes and Transporters
  - No Hepatic First-Pass Metabolism
BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS I:
HIGH SOLUBILITY-HIGH PERMEABILITY

- *in vitro* – *in vivo* correlation generally good
- *but* no way to account for 1st pass metabolism

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS II:
LOW SOLUBILITY-HIGH PERMEABILITY

- rate of absorption limited by dissolution rate
- *in vitro – in vivo* correlation tenuous since many factors may affect dissolution

CLASS III:
HIGH SOLUBILITY-LOW PERMEABILITY

- Intestinal reserve length is marginal.
- If dissolution is rapid, bioavailability will reflect intestinal permeability and transit time.

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY

- *in vitro*–*in vivo* correlation poor
- good bioavailability not expected

THE BOTTOM LINE

CLASS I DRUGS:
HIGH SOLUBILITY-HIGH PERMEABILITY

- *Preferred* as development candidates
- FDA may *waive* repeat *in vivo* testing if initial formulation has good bioavailability*.