

Drug Absorption and Bioavailability

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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**

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

- Acidic Drugs absorbed in the stomach
- Basic Drugs absorbed in the small intestine
- Gastric pH is always acidic

**In Fact, most drug absorption occurs in the
SMALL INTESTINE**

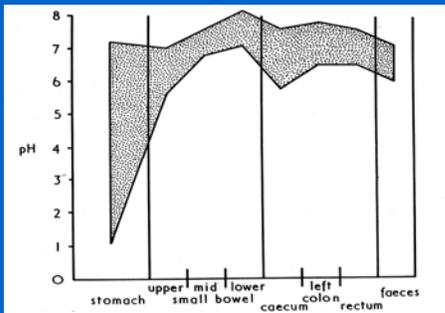
ASPIRIN ABSORPTION FROM STOMACH AND SMALL INTESTINE*

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

pH	ASA ABSORPTION (micromol/100 mg protein/hr)		ASA SERUM LEVEL (mg/100 ml)
	STOMACH	SMALL BOWEL	
3.5	346	469	20.6
6.5	0	424	19.7

* From: Hollander D, et al. J Lab Clin Med 1981;98:591-8

Variation in Gastric and Intestinal pH*



* Meldrum SJ, et al. Br Med J 1972;2:104-6.

PHYSIOLOGICAL FACTORS Affecting Drug Absorption

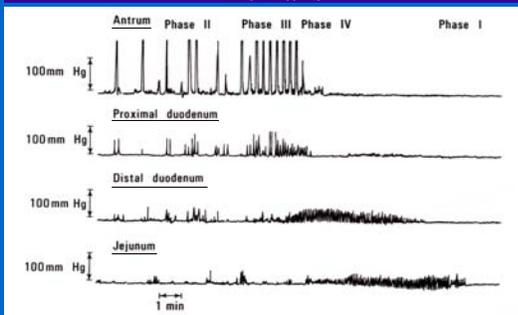
- **Rate of gastric emptying** is a major determinant of *initial delay* in drug absorption.
- **Intestinal motility** is a determinant of the *extent* of drug absorption.

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*



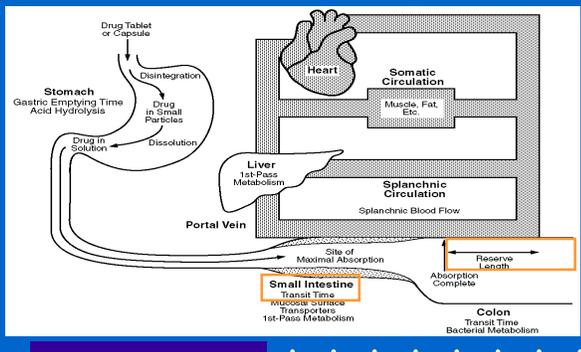
*From: Rees WDW, et al. Dig Dis Sci 1982;27:321-9.

PATTERNS OF GASTRIC MOTOR ACTIVITY

POST PRANDIAL (*Up to 10 hr delay*)

- Pylorus constricted
- Antral contractions reduce particle size

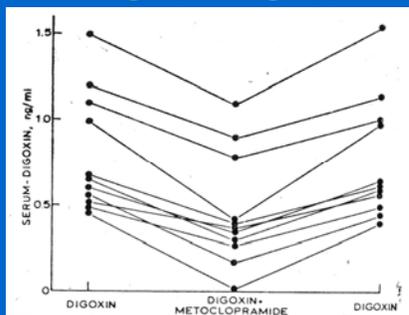
Factors Affecting RATE and EXTENT of Drug Absorption



RESERVE LENGTH

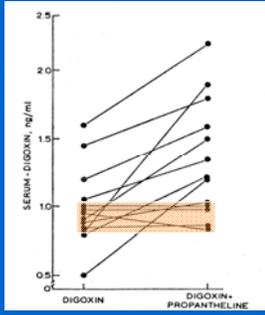
RESERVE LENGTH is the anatomical length over which absorption of a drug *can* occur *MINUS* the length at which absorption is complete.

Effect of METOCLOPRAMIDE on Digoxin Absorption*



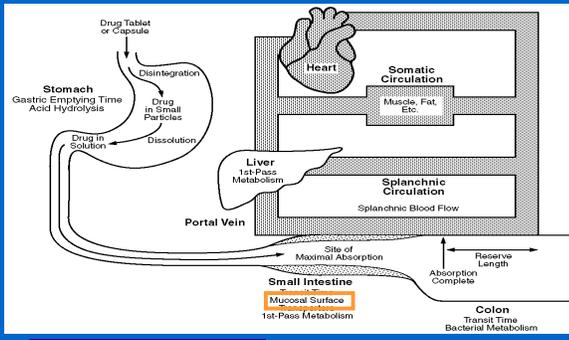
*From: Manninen V, et al. Lancet 1973;1:398-99.

Effect of PROPANTHELINE on Digoxin Absorption*



*From: Manninen V, et al. Lancet 1973;1:398-99.

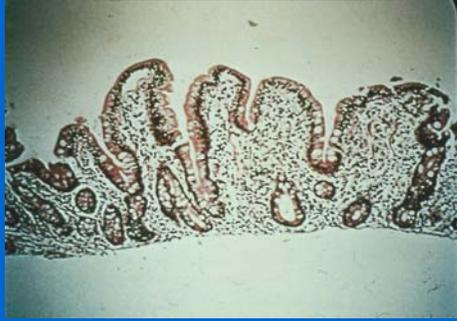
Factors Affecting RATE and EXTENT of Drug Absorption



Normal Intestinal Villi



**Broad Intestinal Villi in a Patient with
SPRUE**



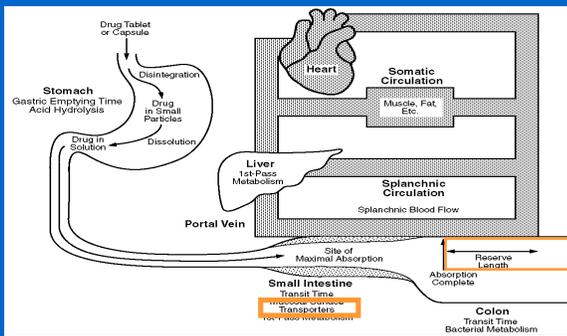
**Digoxin Levels in Patients with
INTESTINAL MALABSORPTION***

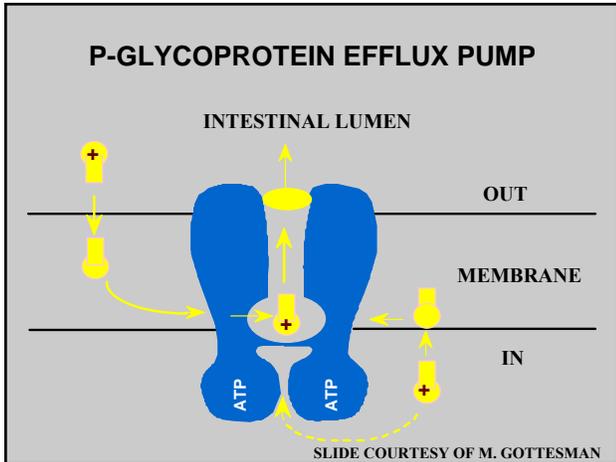
DOSE FOR BOTH GROUPS = 0.25 mg/day.	CONTROLS	MALABSORPTION
[DIGOXIN] (ng/mL)	1.3 ± 0.3	0.4 ± 0.3
URINE D-XYLOSE EXCRETION (gm/5 hr)	5 - 8 [†]	1.1 - 4.1

[†] NORMAL RANGE

* From: Heizer WD, et al. N Engl J Med 1971;285:257-9.

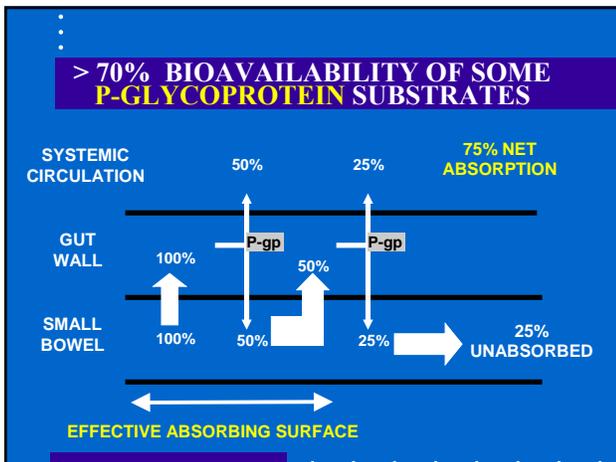
**Factors Affecting RATE and
EXTENT of Drug Absorption**





BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES

> 70% ABSORPTION		30% - 70% ABSORPTION		< 30% ABSORPTION	
DRUG	F %	DRUG	F %	DRUG	F %
PHENOBARBITAL	100	DIGOXIN	70	CYCLOSPORINE	28
LEVOFLOXACIN	99	INDINAVIR	65	TACROLIMUS	25
METHADONE	92	CIMETIDINE	60	MORPHINE	24
PHENYTOIN	90	CLARITHROMYCIN	55	VERAPAMIL	22
METHYLPREDNISOLONE	82	ITRACONAZOLE	55	NICARDIPINE	18
TETRACYCLINE	77	AMITRIPTYLINE	48	SIROLIMUS	15
		DILTIAZEM	38	SAQUINAVIR	13
		ERYTHROMYCIN	35	ATORVASTATIN	12
		CHLORPROMAZINE	32	DOXORUBICIN	5

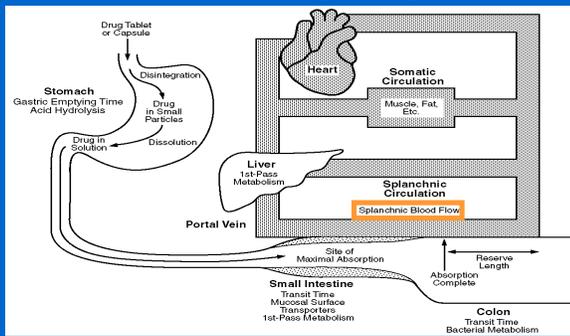


First-Pass Metabolism ± P-Glycoprotein Transport

ALDOSTERONE	MORPHINE*
CYCLOSPORINE*	NORTRIPTYLINE
ISOPROTERENOL	ORGANIC NITRATES
LIDOCAINE	PROPRANOLOL

* Known P-Glycoprotein Substrates

Factors Affecting RATE and EXTENT of Drug Absorption



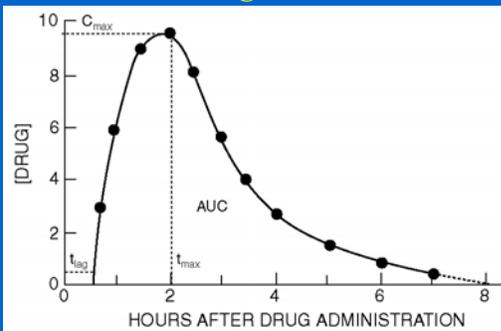
GOALS of Drug Absorption and Bioavailability Lecture

- Factors Affecting Drug Absorption
- **ESTIMATION OF BIOAVAILABILITY**
- Clinical Significance of Differences in Bioavailability
- Prediction of Bioavailability

BIOAVAILABILITY

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

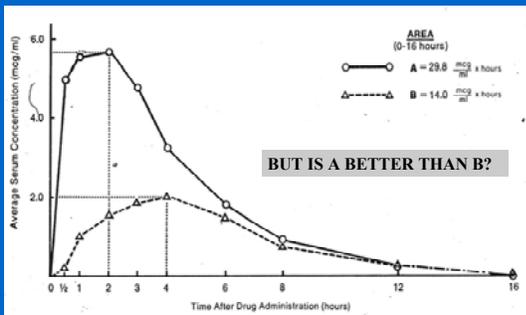
$$dE = CL_E \cdot C dt$$
$$E = CL_E \int_0^{\infty} C dt$$
$$D \cdot F = CL_E \cdot AUC$$

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

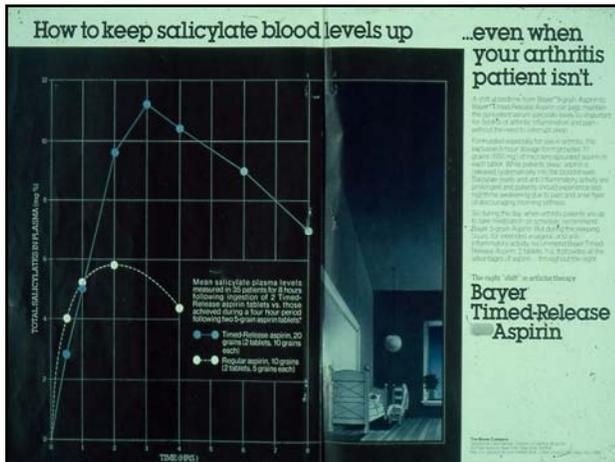
$$\% \text{ Absorption} = \frac{D_{IV} \cdot AUC_{oral}}{D_{oral} \cdot AUC_{IV}} \times 100$$

Comparison here is between an ORAL and an IV Formulation

RELATIVE Bioavailability

$$\% \text{ Relative B.A.} = \frac{D_{\text{Ref.}} \cdot \text{AUC}_{\text{Test}}}{D_{\text{Test}} \cdot \text{AUC}_{\text{Ref.}}} \times 100$$

Comparison here is between
2 ORAL Formulations



RELATIVE Bioavailability

$$\% \text{ Relative B.A.} = \frac{D_{\text{Ref.}} \cdot \text{AUC}_{\text{Test}}}{D_{\text{Test}} \cdot \text{AUC}_{\text{Ref.}}} \times 100$$

AUC Values have to be
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_{MAX}
 - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

Extent of Absorption from Renal Excretion of Unchanged Drug

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

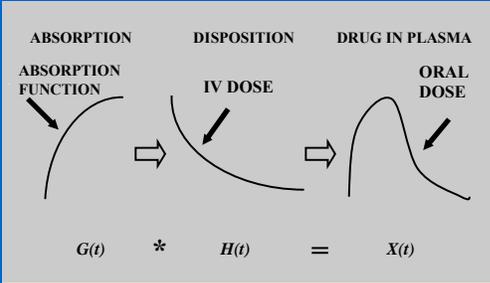
$F \cdot D_{oral} = \left(\frac{CL_E}{CL_R} \right) E_{R(oral)}$ and $D_{IV} = \left(\frac{CL_E}{CL_R} \right) E_{R(IV)}$

So: % Absorption = $\frac{D_{IV} \cdot E_{R(oral)}}{D_{oral} \cdot E_{R(IV)}} \times 100$

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_{MAX}
 - Integrated Pharmacokinetic Analysis of Absolute Bioavailability.

INTERACTION OF DRUG ABSORPTION AND DISPOSITION PROCESSES



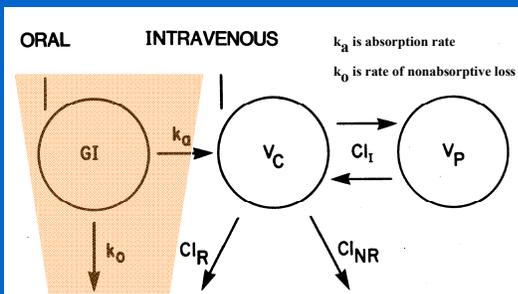
THE OPERATION OF CONVOLUTION

INTEGRAL FORM : $X(t) = \int_0^t G(\tau) \cdot H(t-\tau) d\tau$

TIME DOMAIN : $X(t) = G(t) * H(t)$

SUBSIDIARY EQUATION : $x(s) = g(s) \cdot h(s)$

MODEL Used to Analyze Kinetics of Drug Absorption



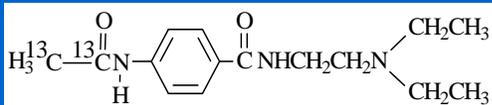
Calculation of Bioavailability from First-Order Absorption Model

$$F = \frac{k_a}{k_a + k_o}$$

Methods for Assessment of ABSOLUTE BIOAVAILABILITY

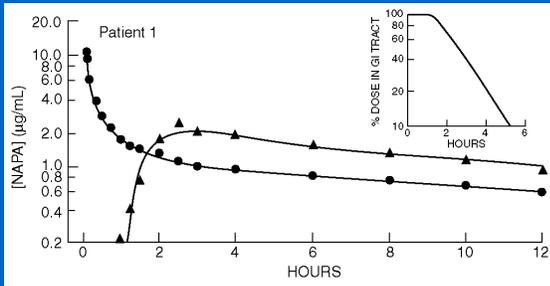
- CONVENTIONAL:
IV and ORAL doses given on **two separate occasions**.
 - Requires two study sessions
 - Requires two sets of blood samples
 - **Assumes no change in disposition** parameters between studies
- STABLE ISOTOPE:
 - **One** study and set of blood samples
 - Special **synthesis** requirements
 - **Mass Spectrometer Assay** required

NAPA-¹³C₂



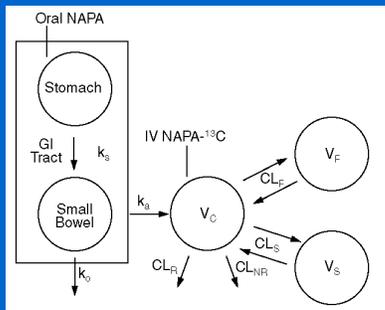
N-ACETYLPROCAINAMIDE (NAPA-¹³C₂)

Simultaneous Administration of Oral NAPA and IV NAPA-C¹³*



* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

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



* From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.

BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

PATIENT NUMBER	KINETIC ANALYSIS (%)	NAPA RECOVERY IN URINE* (%)
1	66.1	65.9
2	92.1	92.1
3	68.1	69.9
4	88.2	73.1
5	75.7	75.6

* Corrected for absorption lag time.

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

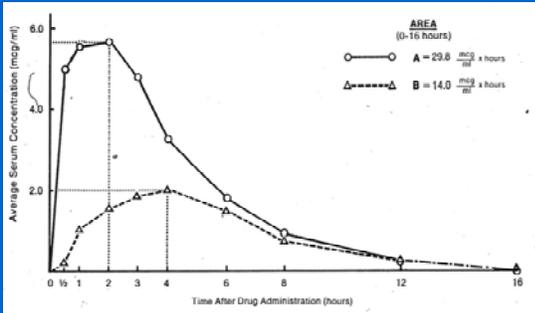
Bioequivalence: AUC and Cmax within 80% - 125% of reference compound.

Bioinequivalence: Greater difference in bioavailability.

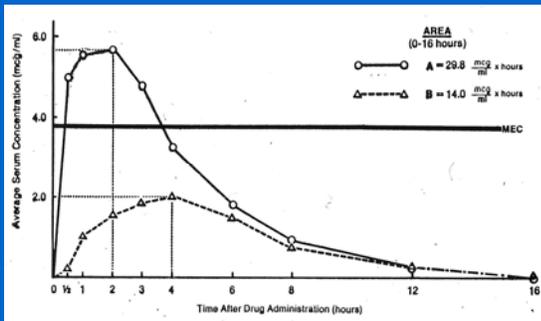
Therapeutic Equivalence: Similar clinical effectiveness and safety.

Therapeutic Inequivalence: Important clinical difference in bioavailability.

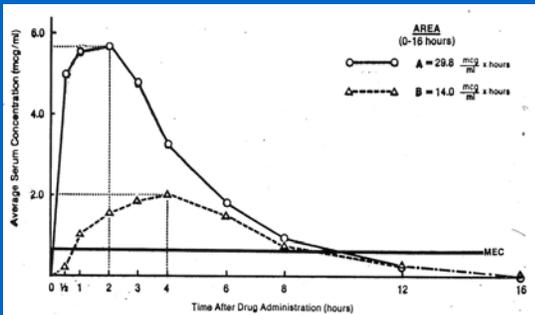
**AUC A > B:
Therapeutic Significance?**



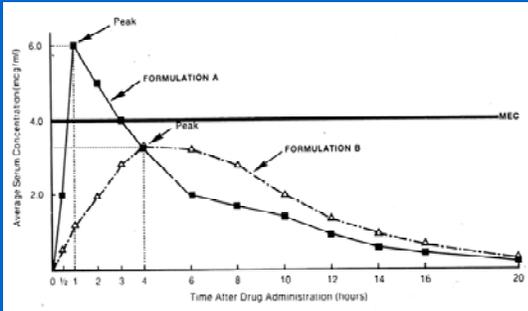
AUC A > B: B Ineffective



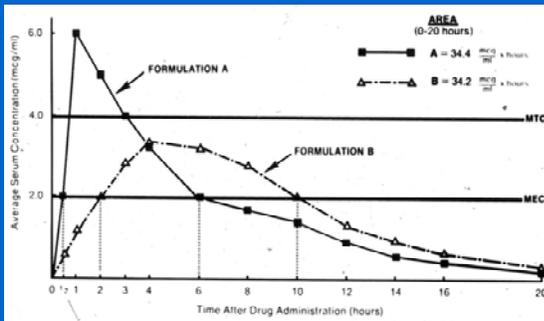
**AUC A > B:
A and B Equally Effective**



**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 *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 *

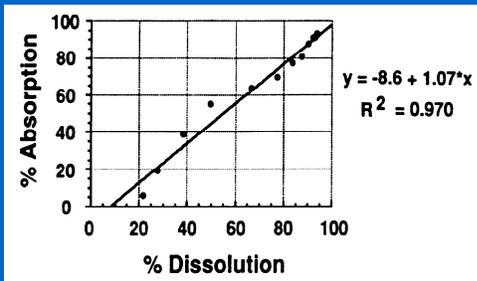
- CLASS I:
High Solubility-High Permeability
- CLASS II:
Low Solubility-High Permeability
- CLASS III:
High Solubility-Low Permeability
- CLASS IV:
Low Solubility-Low Permeability

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

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

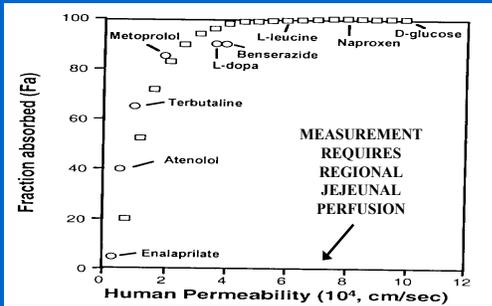


* From Rackley R.J. In Young D, Devane JG, Butler J, eds. In vitro-in vivo correlations. p. 1-15.

Three CRITICAL Biopharmaceutical Properties

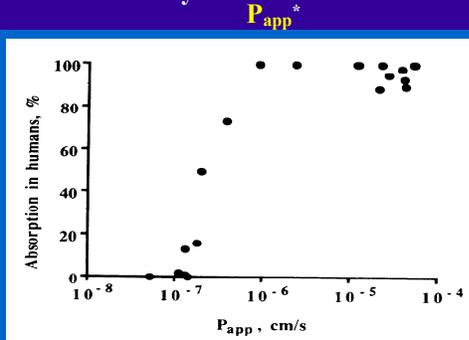
- Drug Solubility *Relative* to Dose
- Dissolution Rate of Formulation
- **INTESTINAL PERMEABILITY** of Drug

Bioavailability vs. Jejeunal Permeability*



* From Amidon GL et al. Pharm Res 1995;12:413-20.

Bioavailability vs. Caco-2 Cell Permeability



* From Arturson P, Karlsson J. Biochem Biophys Res Commun 1991;175:880-5.

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

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

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

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS III:
HIGH SOLUBILITY-LOW PERMEABILITY

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

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

BIOPHARMACEUTIC DRUG CLASSIFICATION *

CLASS IV:
LOW SOLUBILITY-LOW PERMEABILITY

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

* From: Amidon GL, et al. Pharm Res 1995;12:413-20

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*.

* Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, CDER Guidance for Industry, August 2000.
