Drug Absorption and Bioavailability

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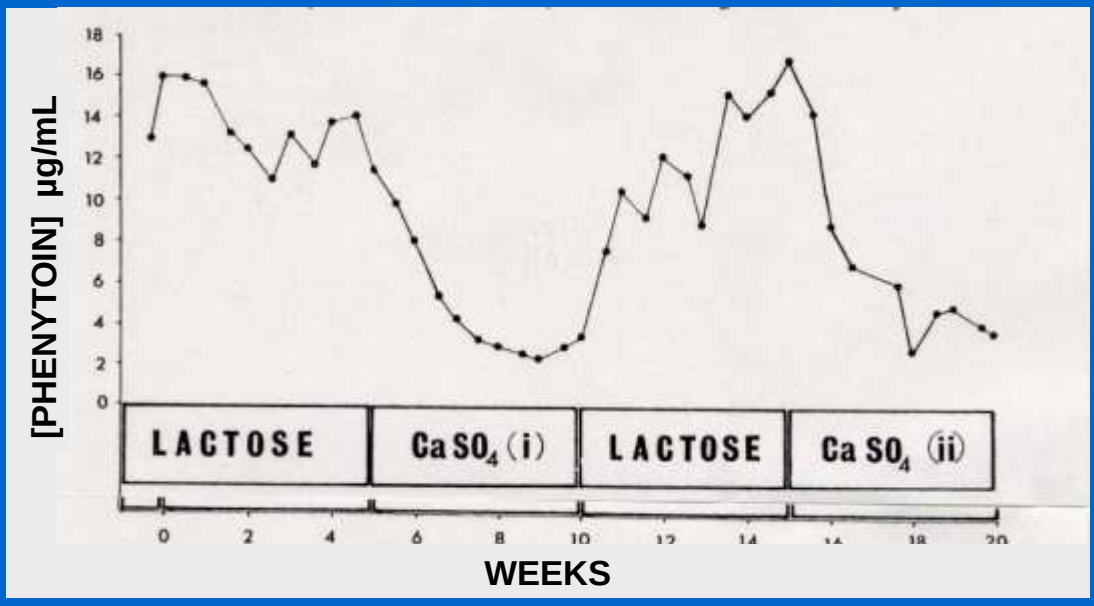
GOALS of Drug Absorption and Bioavailability Lecture

- *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**

Change in PHENYTOIN *Excipients* Results in Epidemic Toxicity*

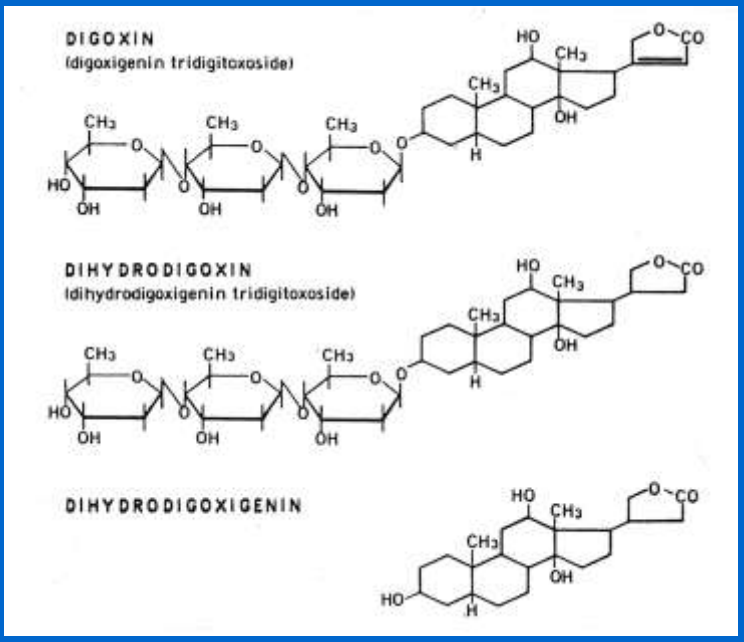


* Bochner F, et al. Proc Aust Assoc Neurol 1973;9:165-70

Factors Affecting DRUG ABSORPTION

- Biopharmaceutic Factors
- INTERACTIONS
  - Food
  - Other Drugs
  - Bacteria
- Physiologic Factors

ENTERIC METABOLISM OF DIGOXIN*



*** Lindenbaum J, et al. N Engl J Med 1981;305:789-94.**

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

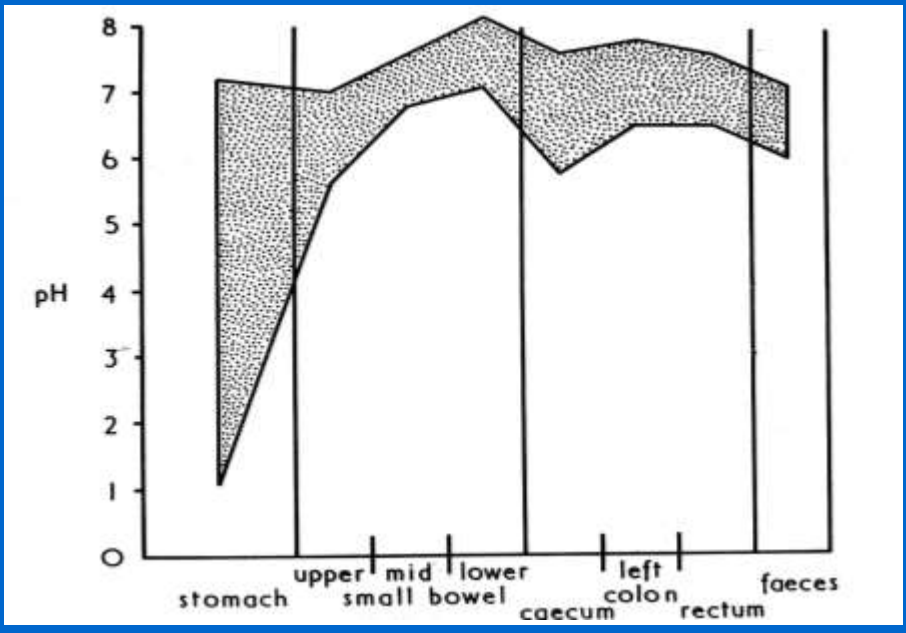
In Fact, most drug absorption occurs in the SMALL INTESTINE

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)*

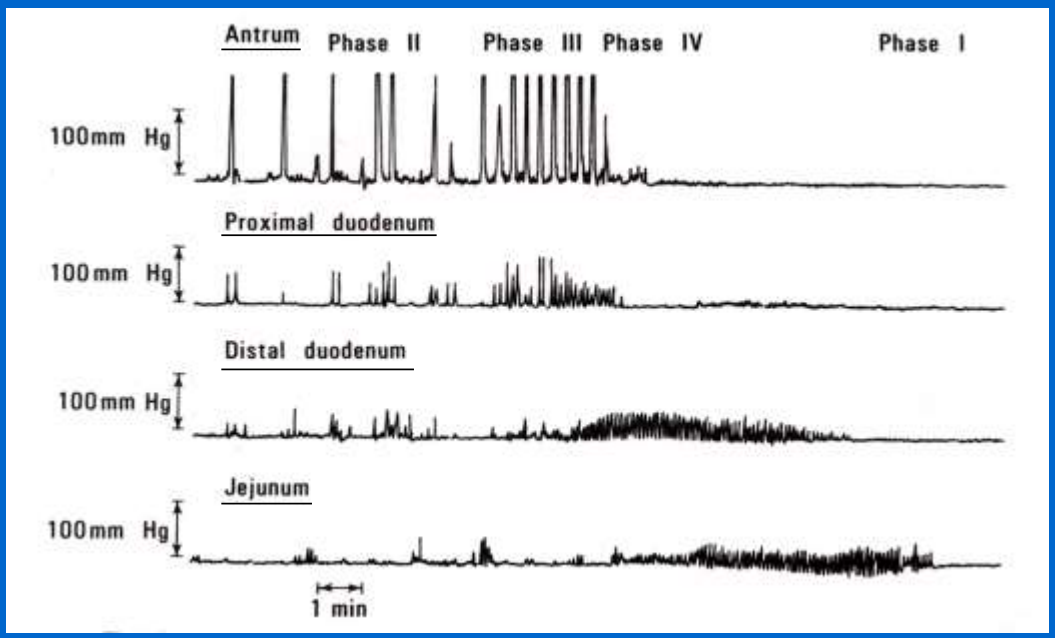
Phase 1 - Quiescence

Phase 2 - Irregular Contractions

Phase 3 - Major Motor Complex Burst

Phase 4 - Transition Period

Interdigestive Intestinal Motor Activity in Humans*



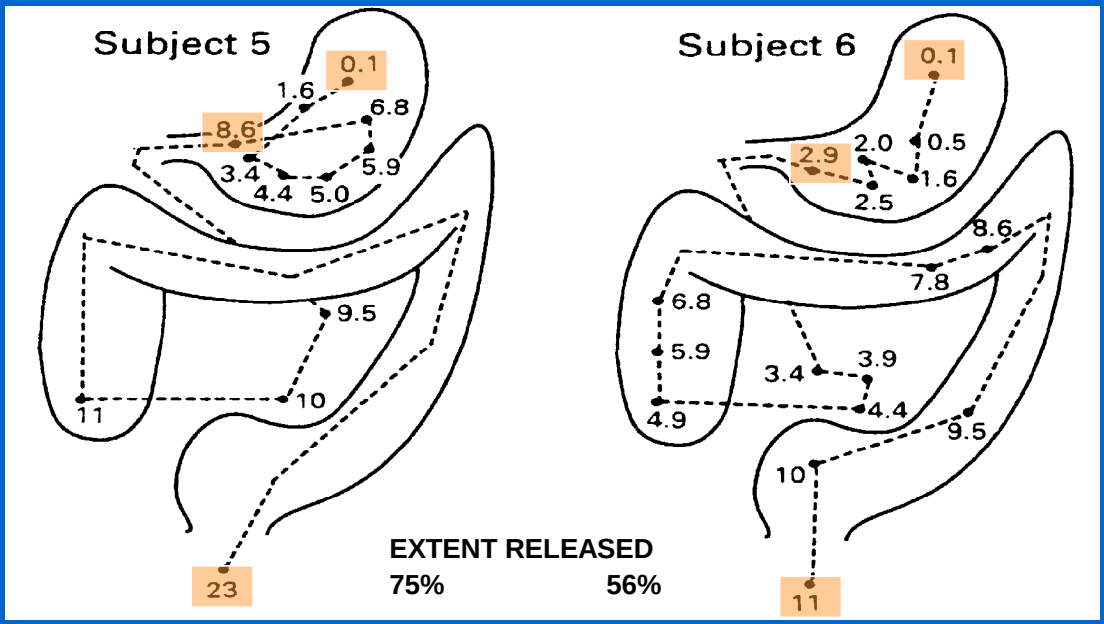
*From: Rees WDW, et al. Dig Dis Sci 1982;27:321-9.

PATTERNS OF GASTRIC MOTOR ACTIVITY

POST PRANDIAL (*Up to 10 hr delay*)

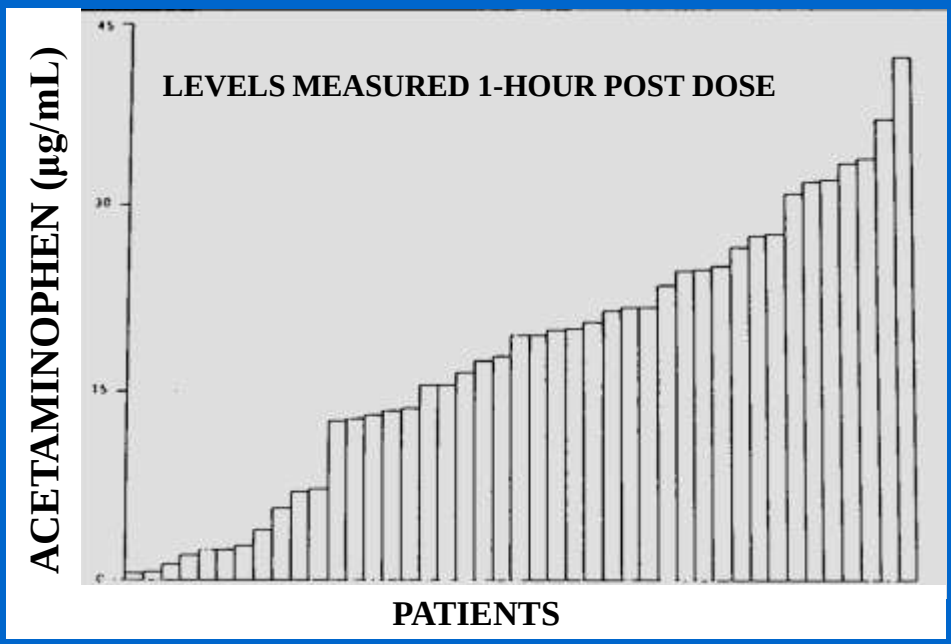
- **Pylorus constricted**
- **Antral contractions reduce particle size**

*GI TRANSIT - SUSTAINED-RELEASE CARBAMAZEPINE FORMULATION**



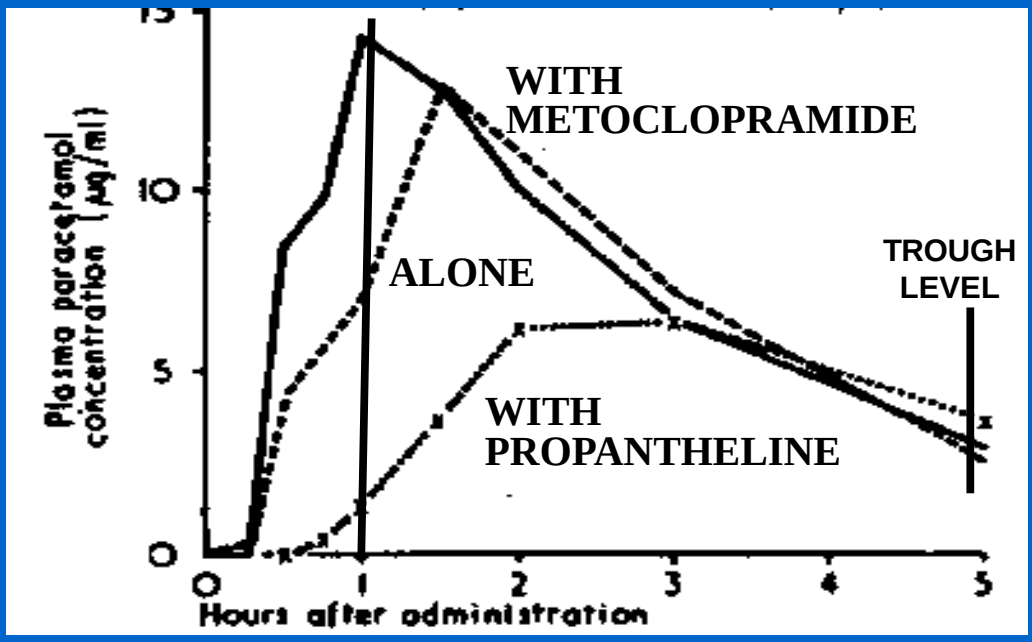
*From: Wilding IR, et al. Br J Clin Pharmacol 1991;32:573-9.

Variation in "Peak" Levels
ACETAMINOPHEN*



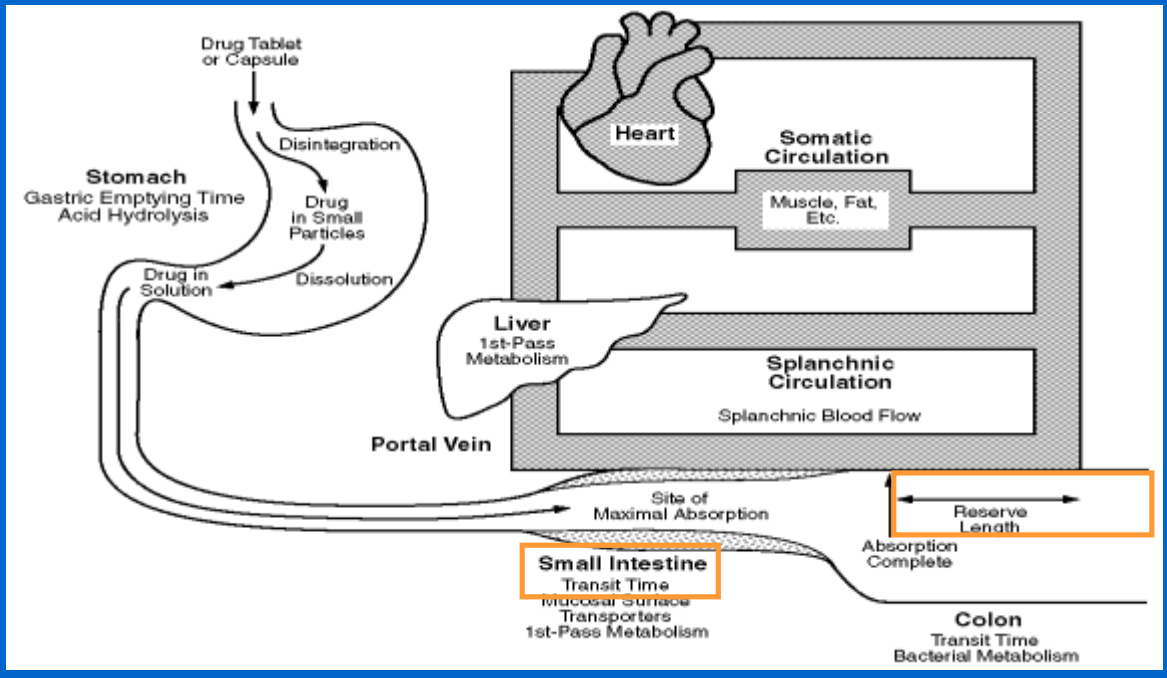
* Prescott LF. Med Clin N Am 1974;42:907-16.

Gastric Emptying Rate Affects ACETAMINOPHEN Absorption*



*From: Nimmo J, et al. Br Med J 1973;1:587-9.

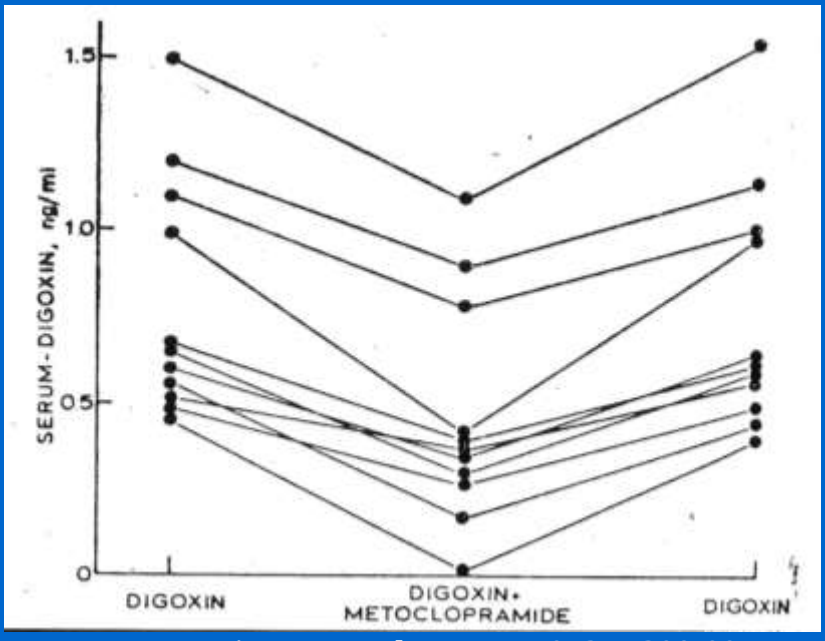
Factors Affecting RATE and EXTENT of Drug Absorption



RESERVE LENGTH

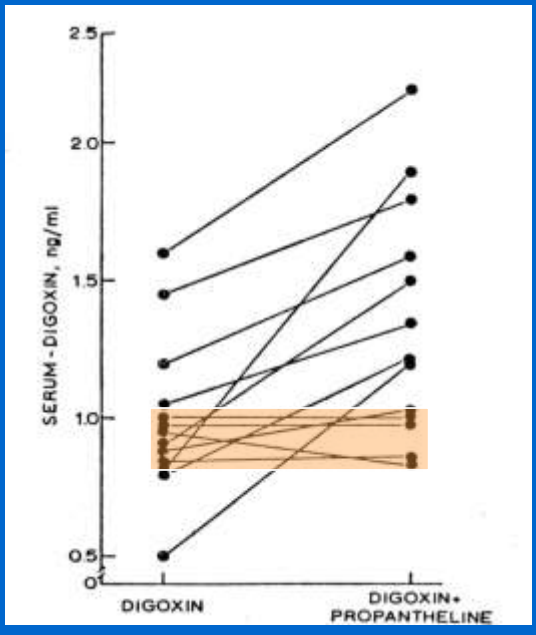
RESERVE LENGTH **is the anatomical length over which absorption of a drug *can* occur *MINUS* the length at which absorption is complete.**

Effect of METOCLOPRAMIDE on Digoxin Absorption*



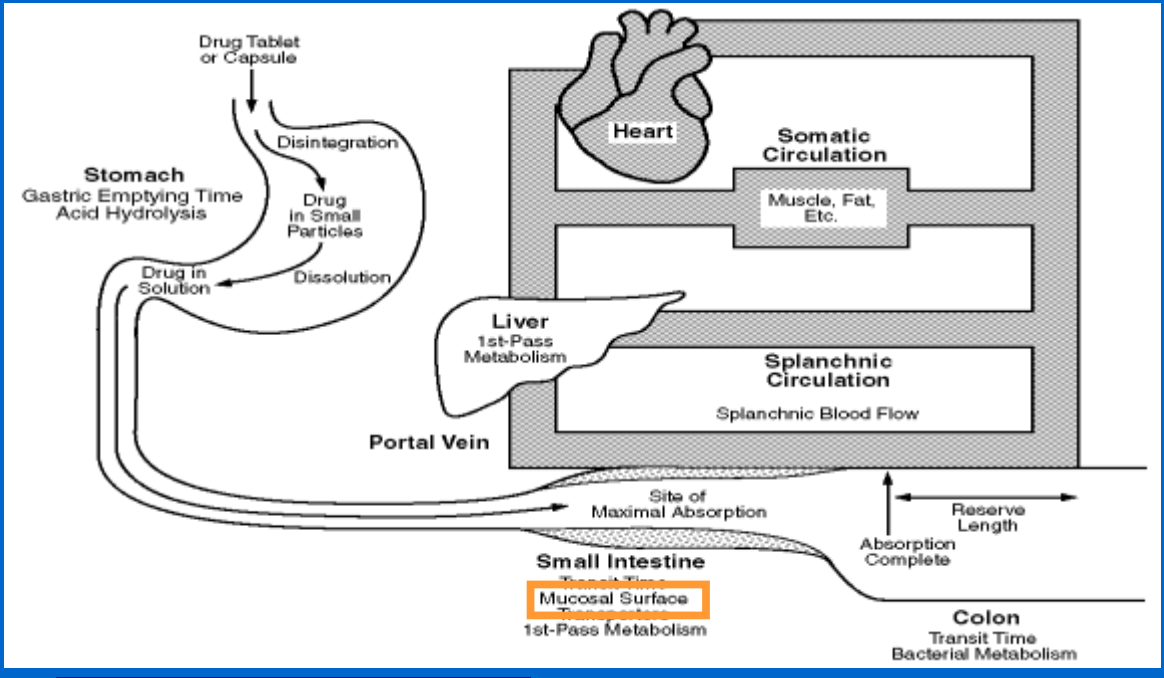
*From: Manninen V, et al. Lancet 1973;1:398-99.

Effect of PROPANTHELINE on Digoxin Absorption*



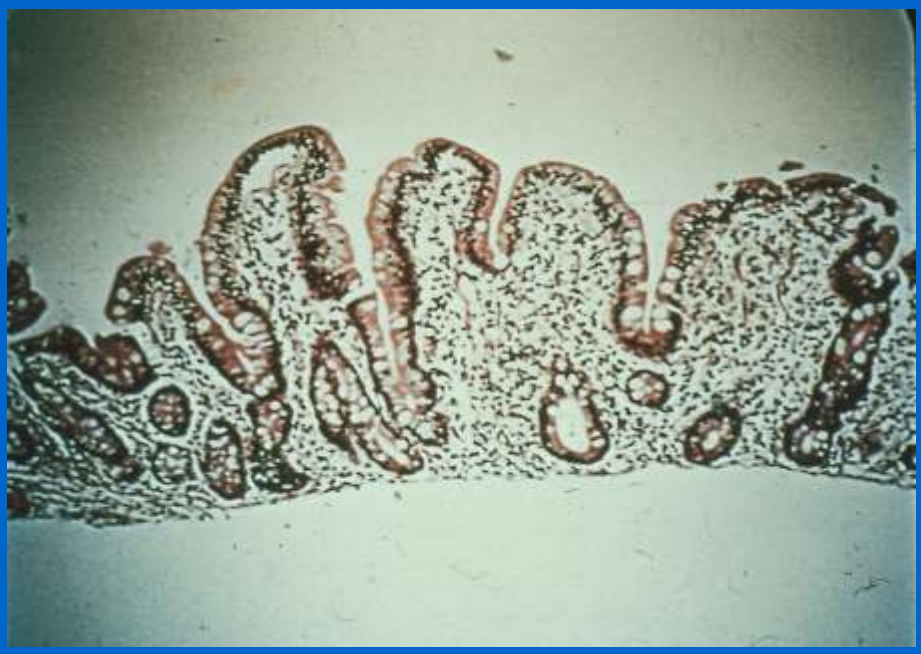
*From: Manninen V, et al. Lancet 1973;1:398-99.

Factors Affecting RATE and EXTENT of Drug Absorption



Normal Intestinal Villi

Broad Intestinal Villi in a Patient with SPRUE



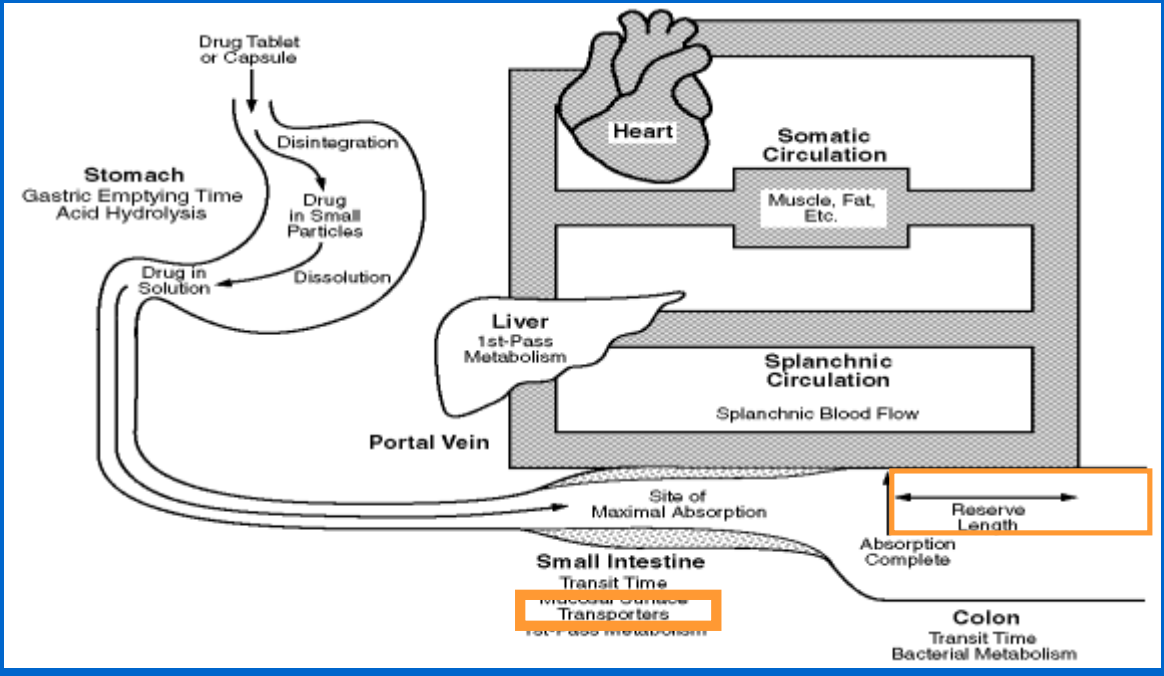
Digoxin Levels in Patients with INTESTINAL MALABSORPTION*

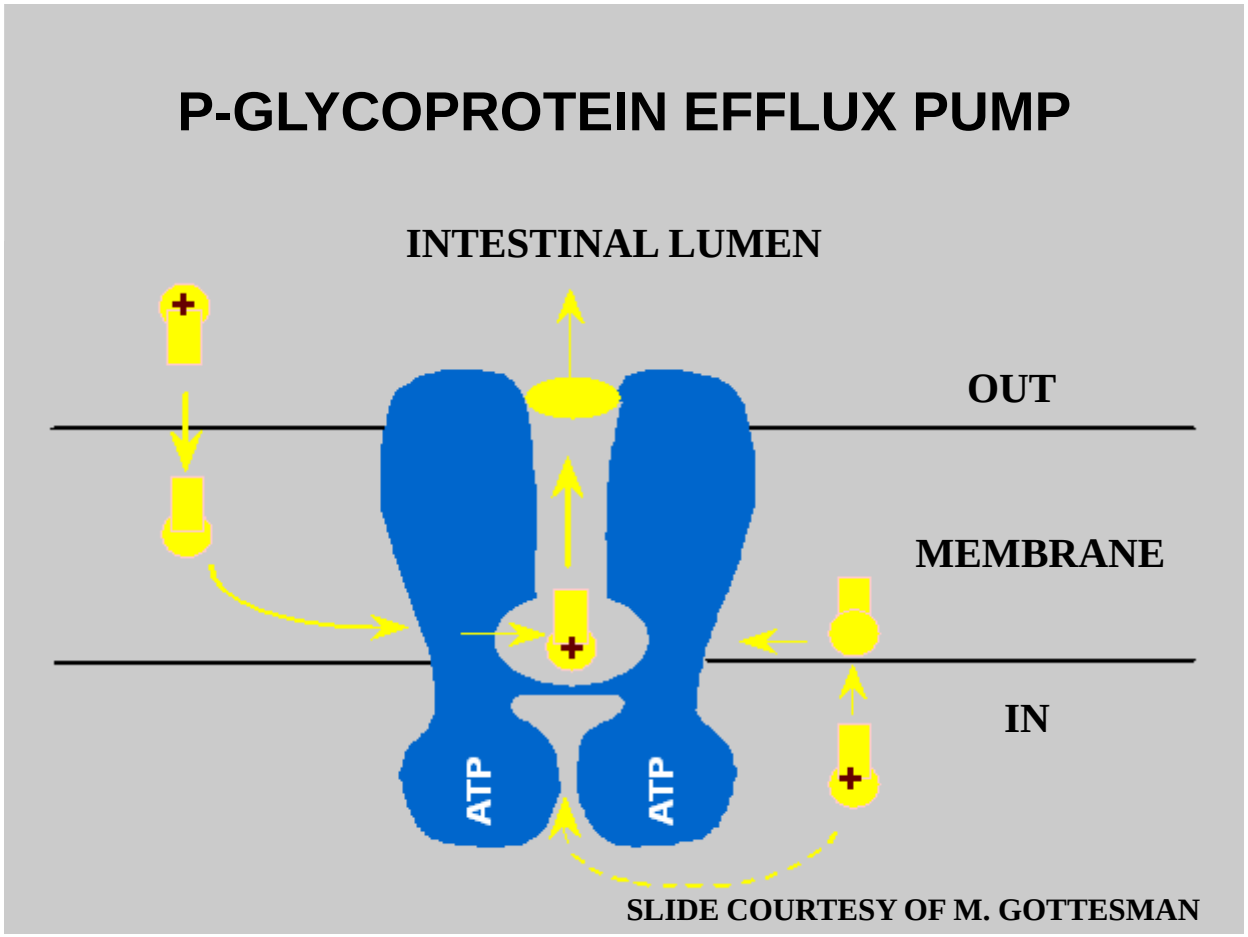
DOSE FOR BOTH GROUPS = 0.25 mg/day.	CONTROLS	MALABSORPTION
[DIGOXIN] (ng/mL)	1.3 ± 0.3	0.4 ± 0.3
URINE D-XYLOSE EXCRETION (gm/5 hr)	5 – 8†	1.1 – 4.1

† NORMAL RANGE

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

Factors Affecting RATE and EXTENT of Drug Absorption

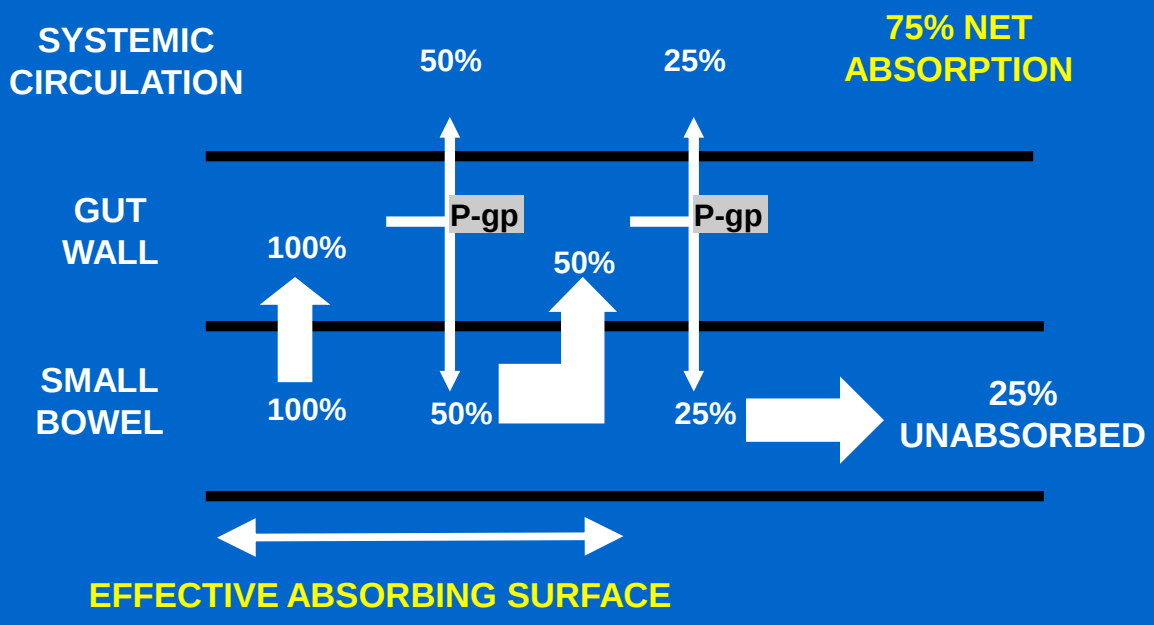



P-GLYCOPROTEIN EFFLUX PUMP
INTESTINAL LUMEN
OUT
MEMBRANE
IN
ATP
ATP
SLIDE COURTESY OF M. GOTTESMAN

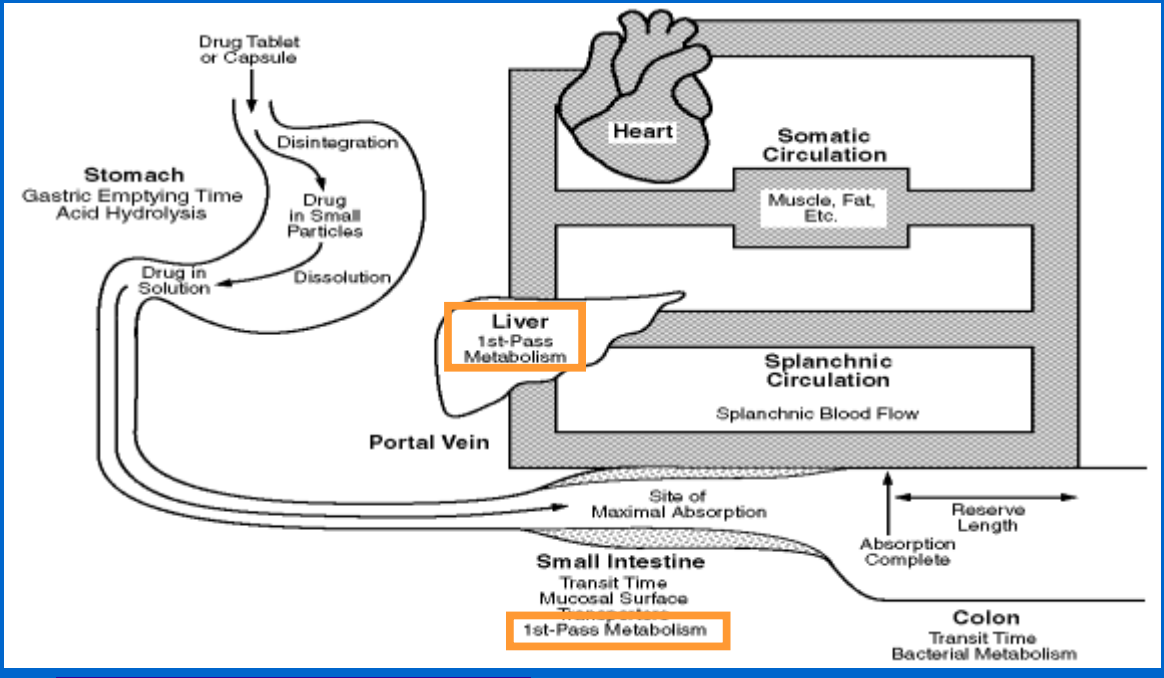
BIOAVAILABILITY OF SOME *P-GLYCOPROTEIN* *SUBSTRATES*

> 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

> 70% BIOAVAILABILITY OF SOME P-GLYCOPROTEIN SUBSTRATES



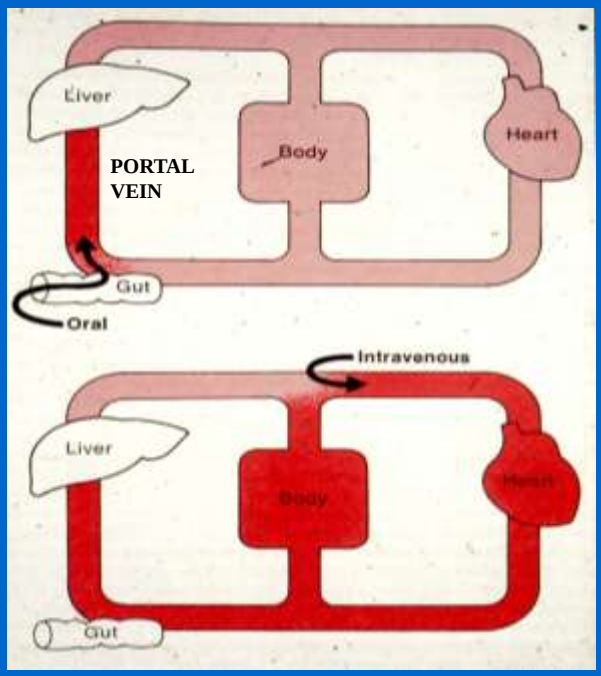
FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION



Sites of FIRST-PASS Elimination

- **INTESTINAL MUCOSA**
  - CYP Enzymes
  - P-Glycoprotein
- **LIVER**
  - CYP Enzymes

FIRST-PASS METABOLISM

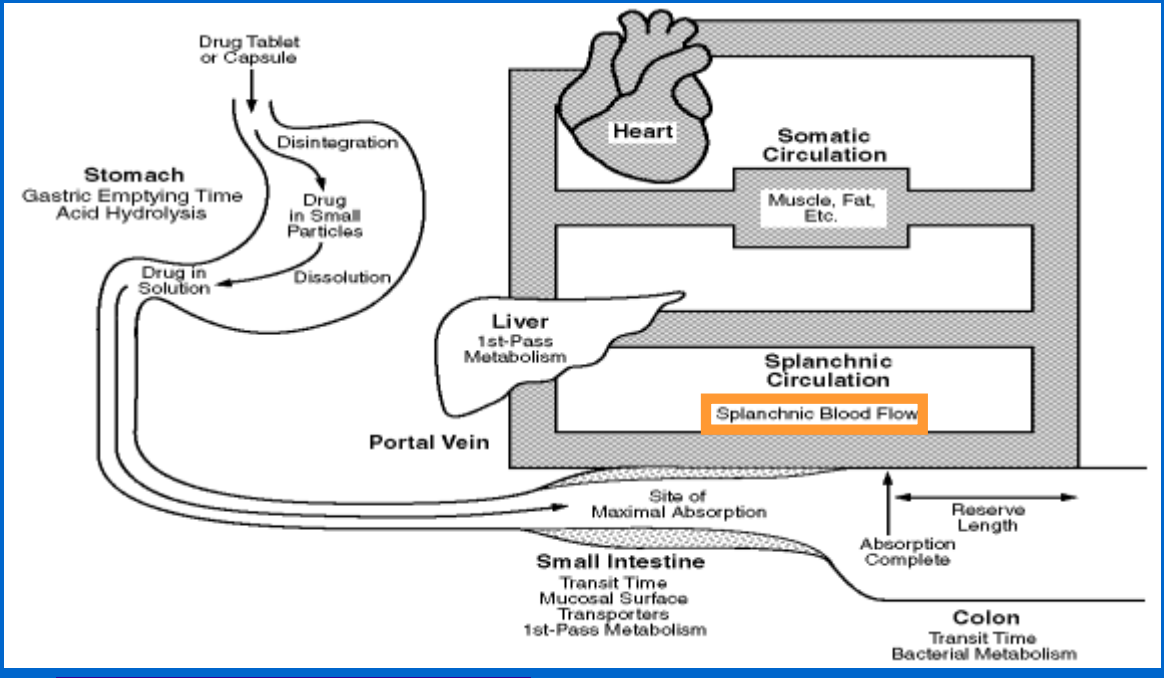


First-Pass Metabolism
P-Glycoprotein Transport

ALDOSTERONE	MORPHINE*
CYCLOSPORINE*	NORTRIPTYLINE
ISOPROTERENOL	ORGANIC NITRATES
LIDOCAINE	PROPRANOLOL

* Known P-Glycoprotein Substrates

Factors Affecting RATE and EXTENT of Drug Absorption



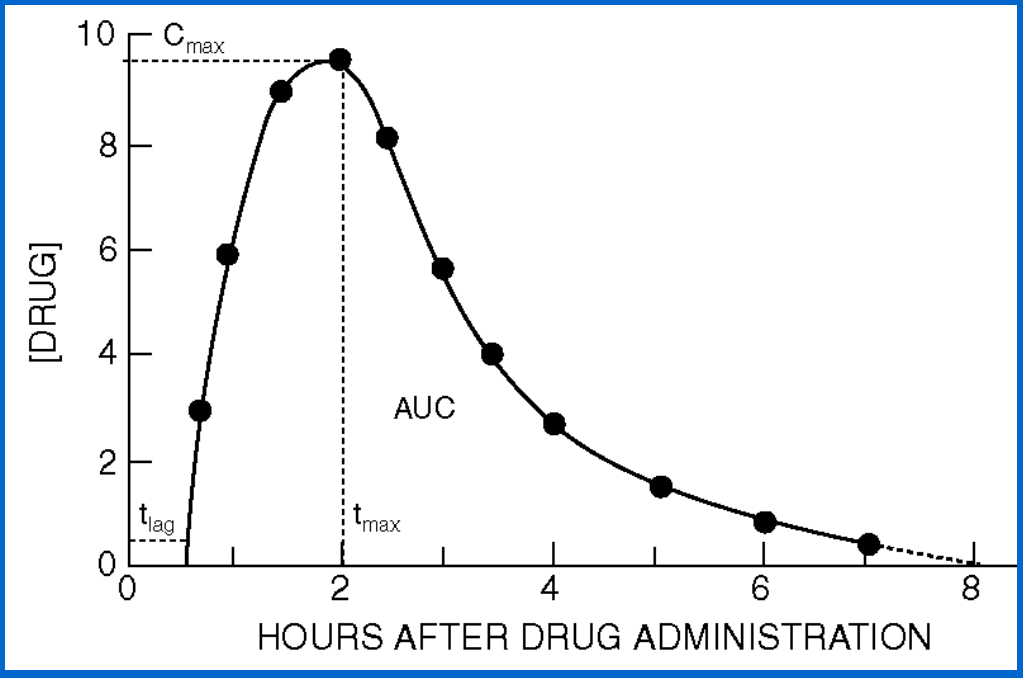
GOALS of Drug Absorption and Bioavailability Lecture

- 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



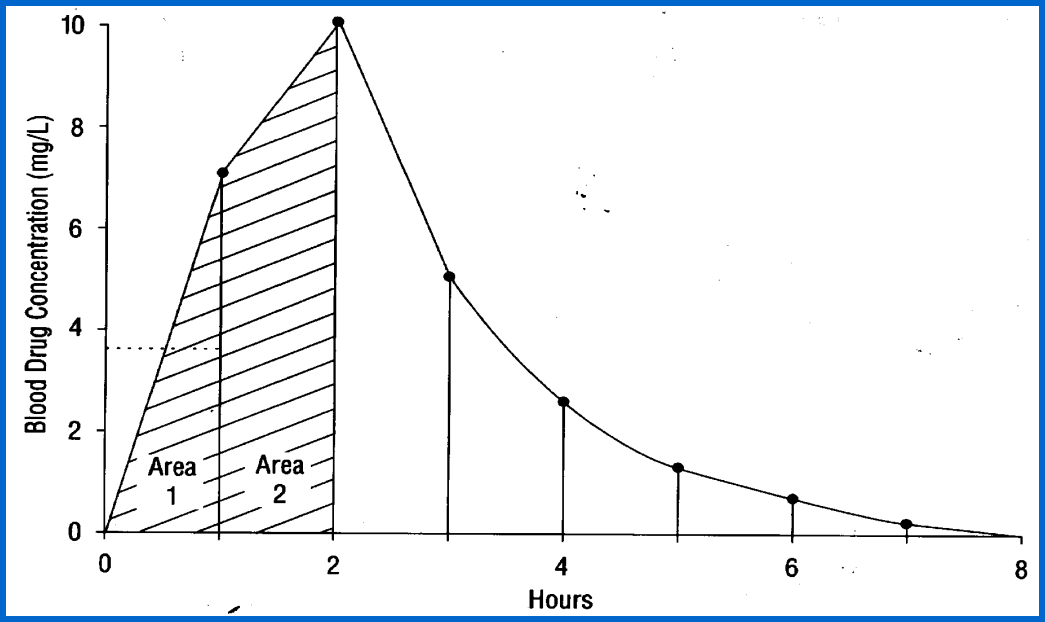
Significance of AUC

$$dE = CL_E \bullet C\, dt$$

$$E = CL_E \int_0^{\infty} C\ dt$$

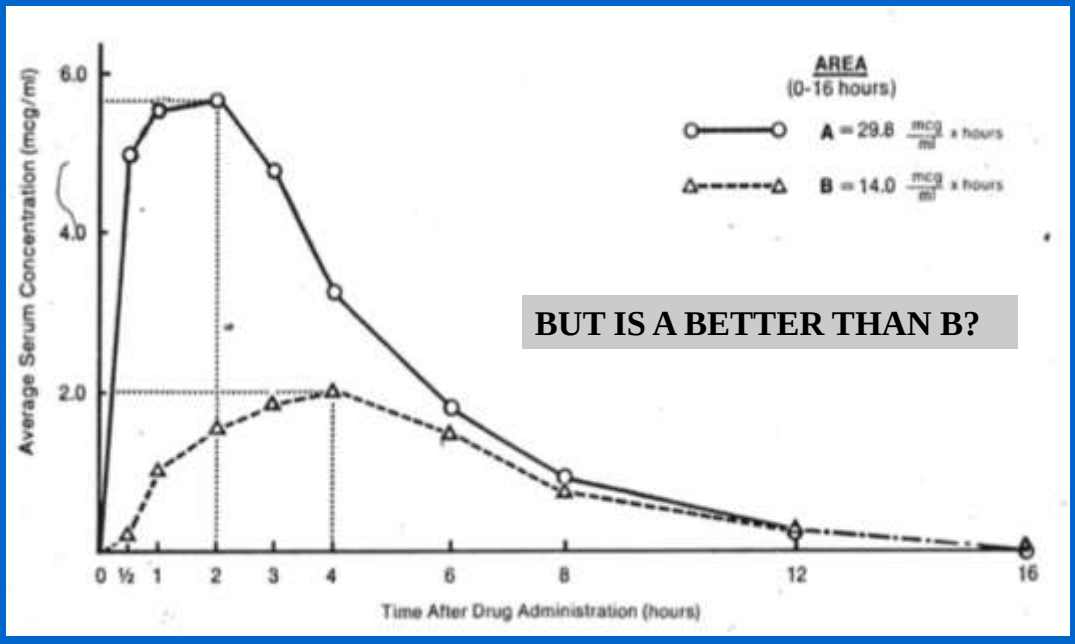
$$D \bullet F = CL_E \bullet AUC$$

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

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

Comparison here is between an ORAL and an IV Formulation

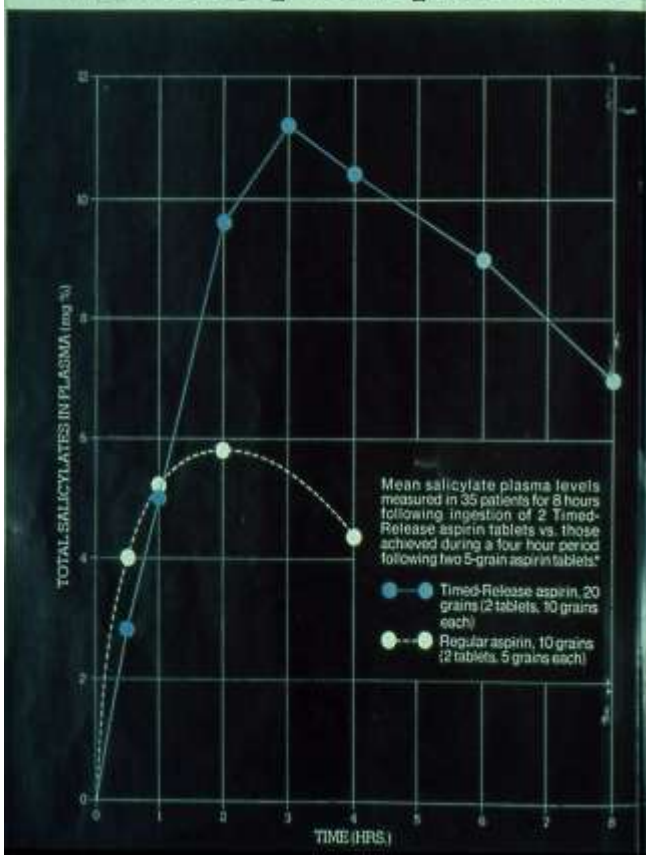
RELATIVE Bioavailability

$$\%\ \text{Relative B.A.} = \frac{D_{\text{Ref.}} \bullet AUC_{\text{Test}}}{D_{\text{Test}} \bullet AUC_{\text{Ref.}}} \times 100$$

Comparison here is between

2 ORAL Formulations

How to keep salicylate blood levels up



...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 consistent serum salicylate levels so important for control of arthritic inflammation and pain without the need to interrupt sleep.

Formulated especially for use in arthritis, this eight-hour 6-hour 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 arise freer of discouraging morning stiffness.

So during the day, when arthritic 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, h.s. 8 provides all the advantages of aspirin – throughout the night.

The right "shift" in arthritis therapy

Bayer Timed-Release Aspirin

RELATIVE Bioavailability

$$\%\ \text{Relative B.A.} = \frac{D_{Ref.} \bullet AUC_{Test}}{D_{Test} \bullet AUC_{Ref.}} \times 100$$

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

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

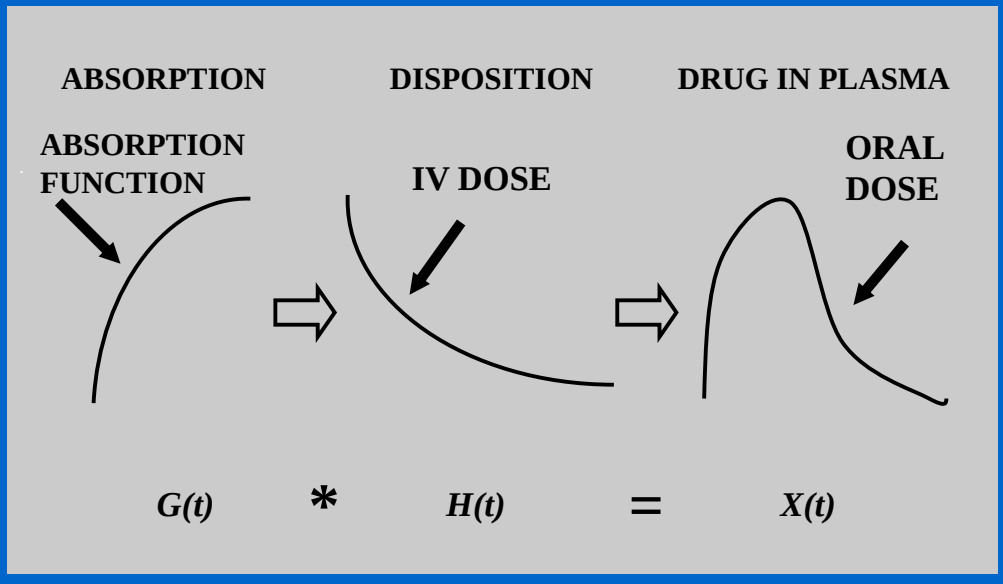
$$F \bullet D_{oral} = \left(\frac{CL_E}{CL_R} \right) E_{R\,(oral)} \quad \text{and} \quad D_{IV} = \left(\frac{CL_E}{CL_R} \right) E_{R\,(IV)}$$

$$\text{So : \% Absorption} = \frac{D_{IV} \bullet E_{R\,(oral)}}{D_{oral} \bullet E_{R\,(IV)}} \text{ X } 100$$

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



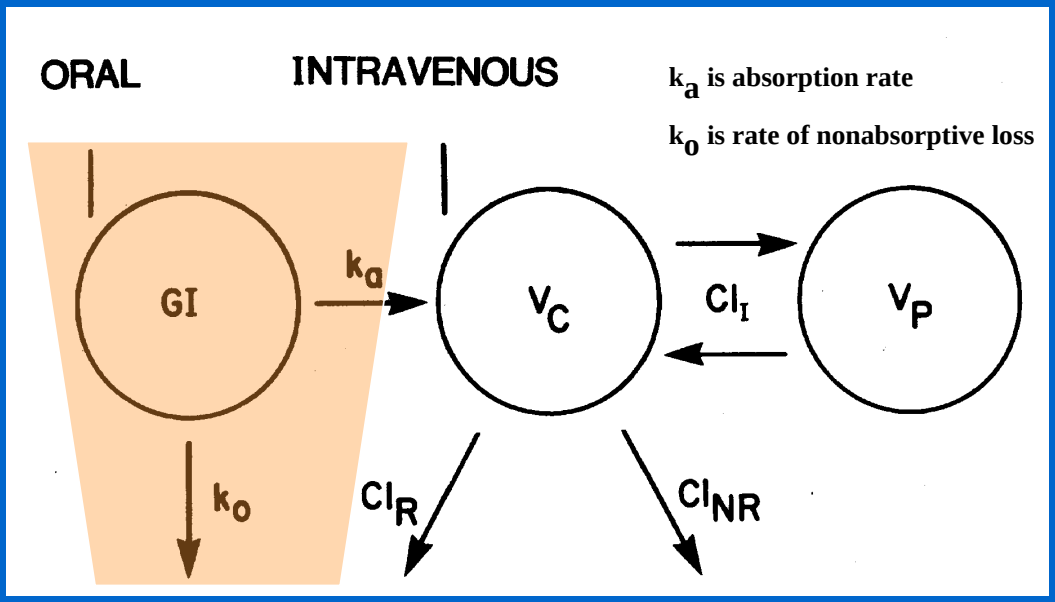
THE OPERATION OF CONVOLUTION

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

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

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

MODEL Used to Analyze Kinetics of Drug Absorption



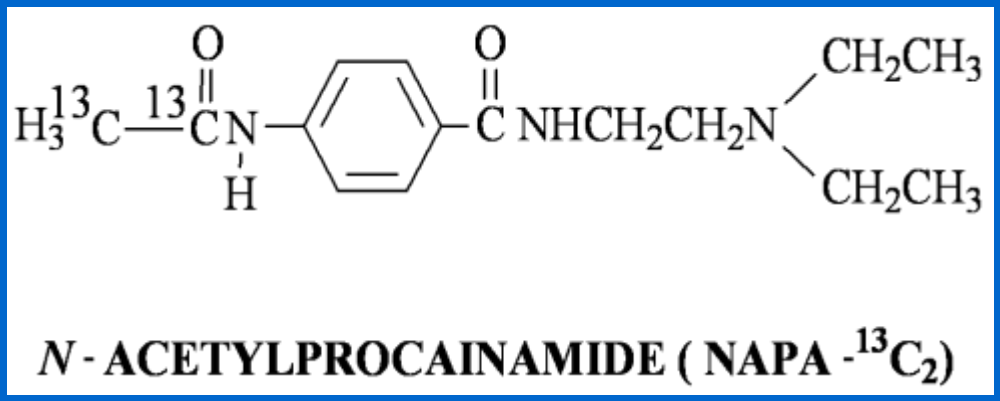
Calculation of Bioavailability from First-Order Absorption Model

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

Methods for Assessment of *ABSOLUTE* BIOAVAILABILITY

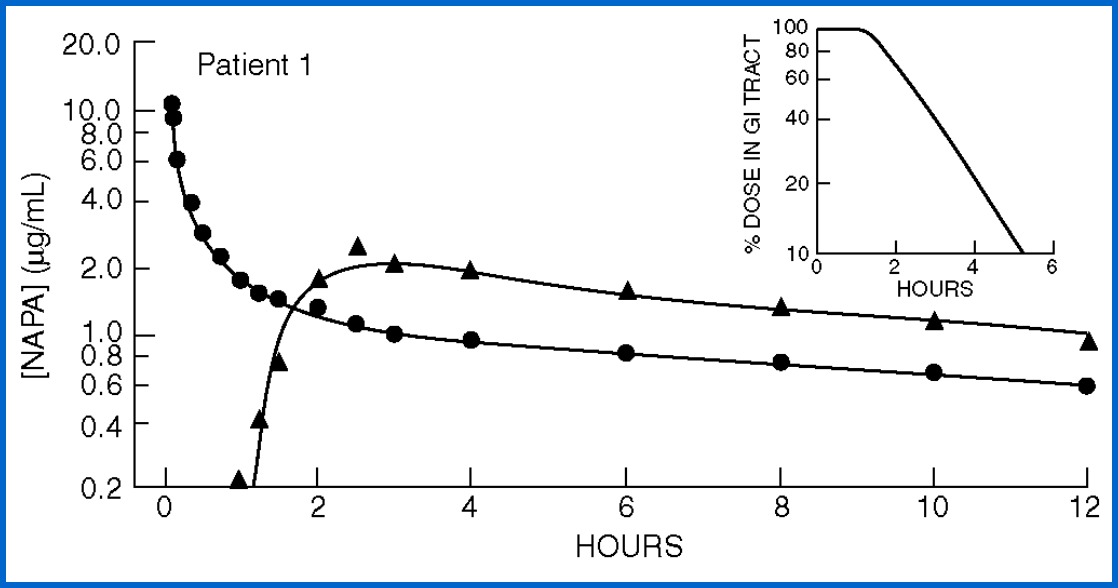
- **CONVENTIONAL:**
  IV and ORAL doses given on two separate occasions.
  - **Requires two study sessions**
  - **Requires two sets of blood samples**
  - **Assumes no change in disposition parameters between studies**
- **STABLE ISOTOPE:**
  - **One study and set of blood samples**
  - **Special synthesis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

NAPA-$^{13}C_2$



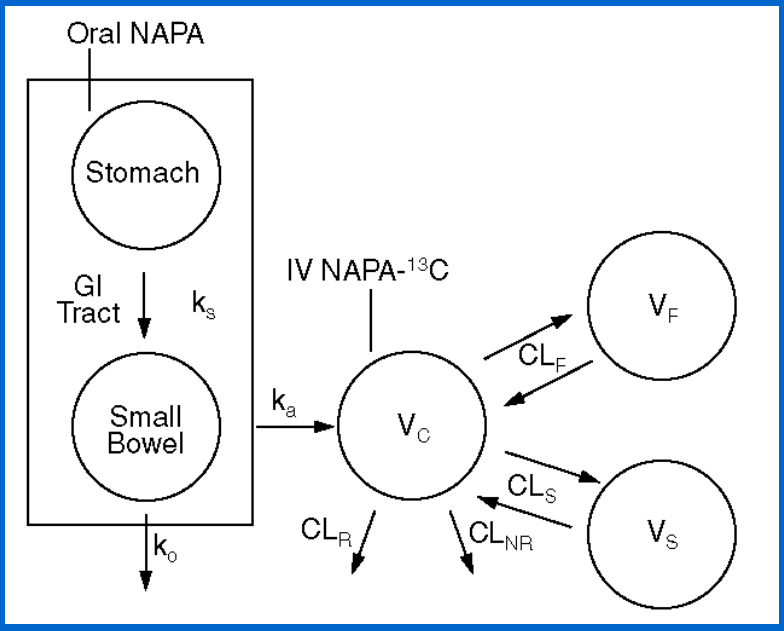
N - ACETYLPROCAINAMIDE (NAPA -$^{13}C_2$)

Simultaneous Administration of Oral NAPA and IV NAPA-C^{13}*



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

MODEL Used to Analyze Oral NAPA and IV NAPA-C^{13} Kinetics*



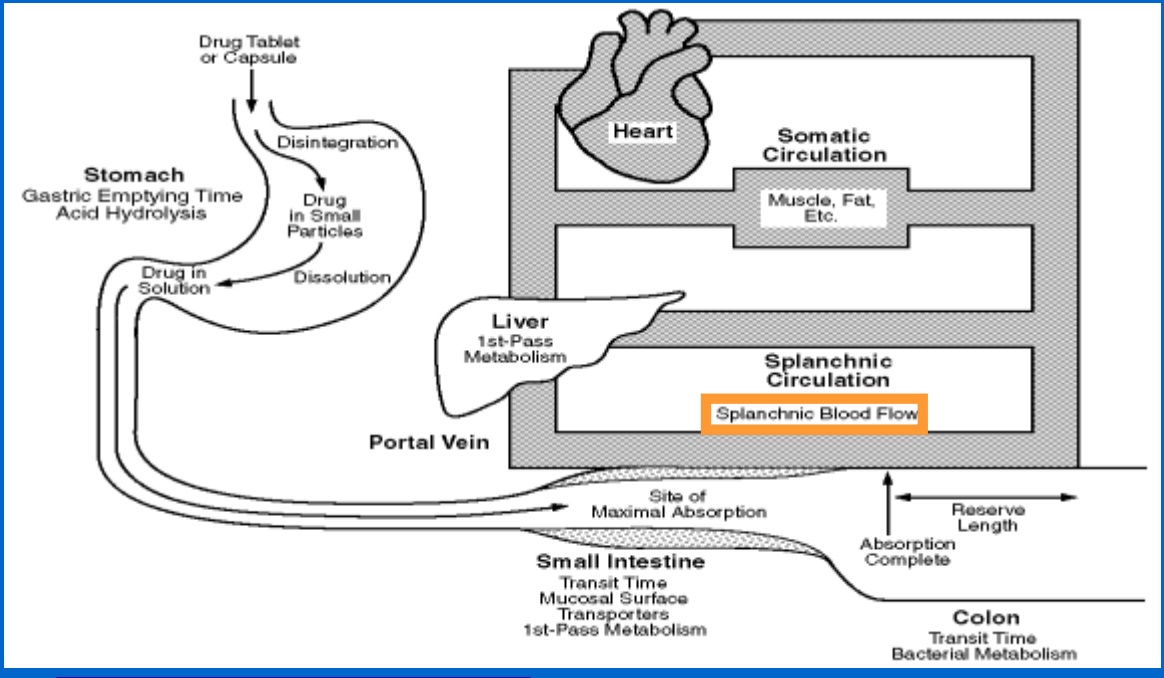
*** From Atkinson AJ Jr, et al. Clin Pharmacol Ther 1989;46:182-9.**

BIOAVAILABILITY Estimates From Kinetic Analysis and URINE RECOVERY

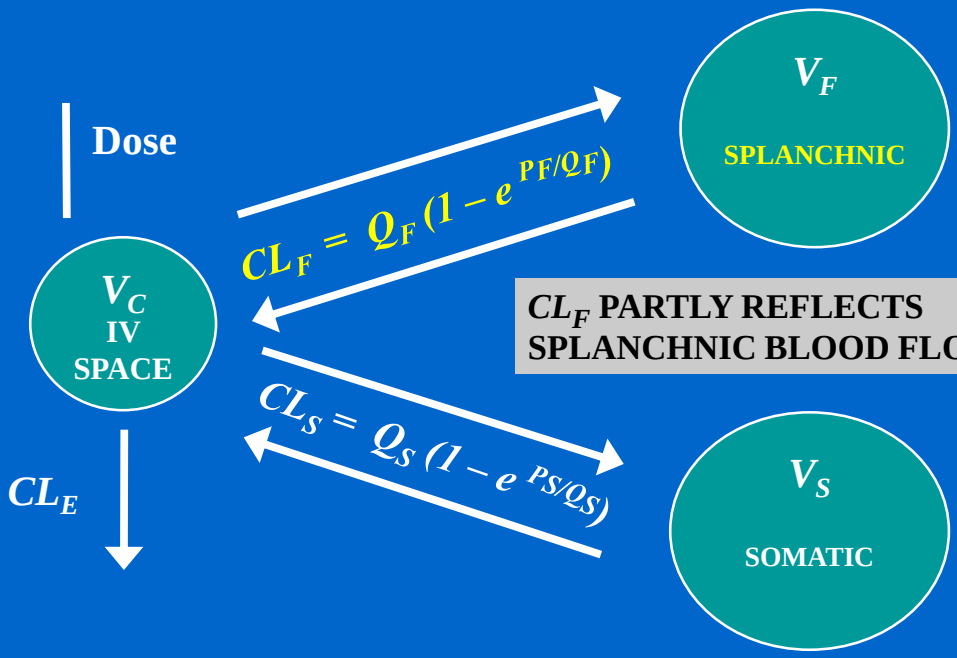
PATIENT NUMBER	KINETIC ANALYSIS (%)	NAPA RECOVERY IN URINE* (%)
1	66.1	65.9
2	92.1	92.1
3	68.1	69.9
4	88.2	73.1
5	75.7	75.6

* Corrected for absorption lag time.

Factors Affecting RATE and EXTENT of Drug Absorption

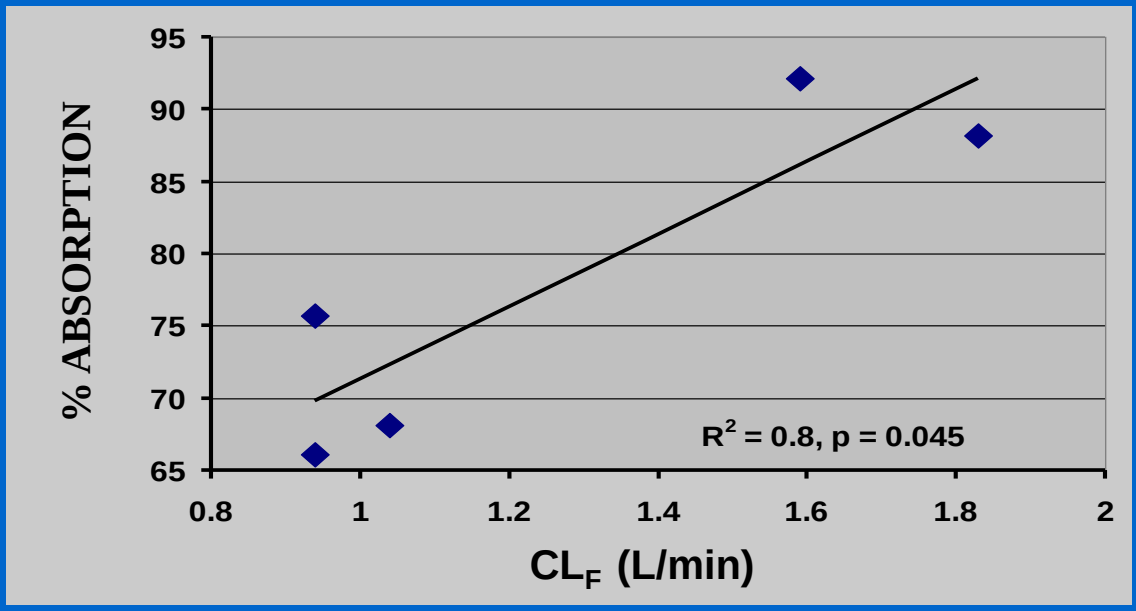


NAPA PK Model After IV Dose



***CL_F* PARTLY REFLECTS SPLANCHNIC BLOOD FLOW**

Relationship Between CL_F and Extent of NAPA Absorption*



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

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

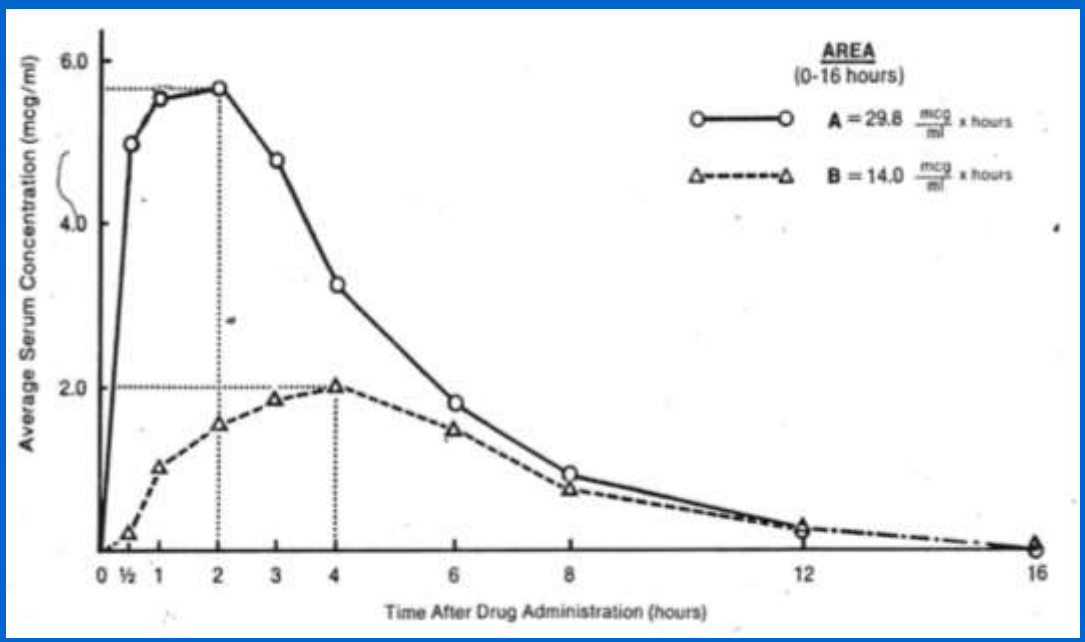
Bioequivalence: AUC and Cmax within 80% - 125% of reference compound.

Bioinequivalence: Greater difference in bioavailability.

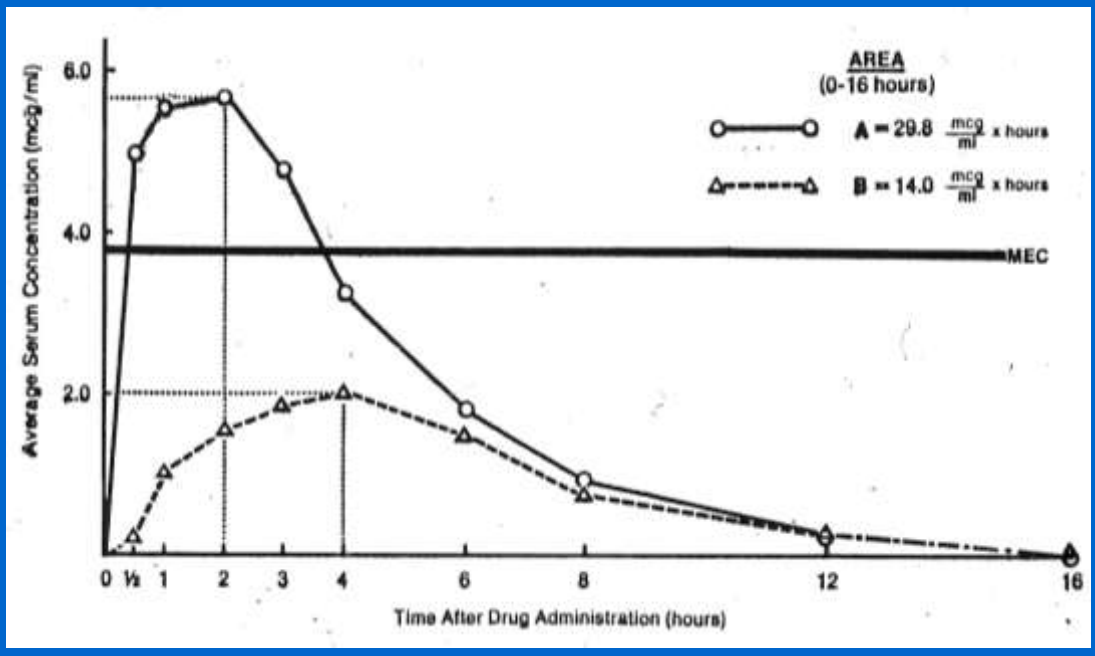
Therapeutic Equivalence: Similar clinical effectiveness and safety.

Therapeutic Inequivalence: Important clinical difference in bioavailability.

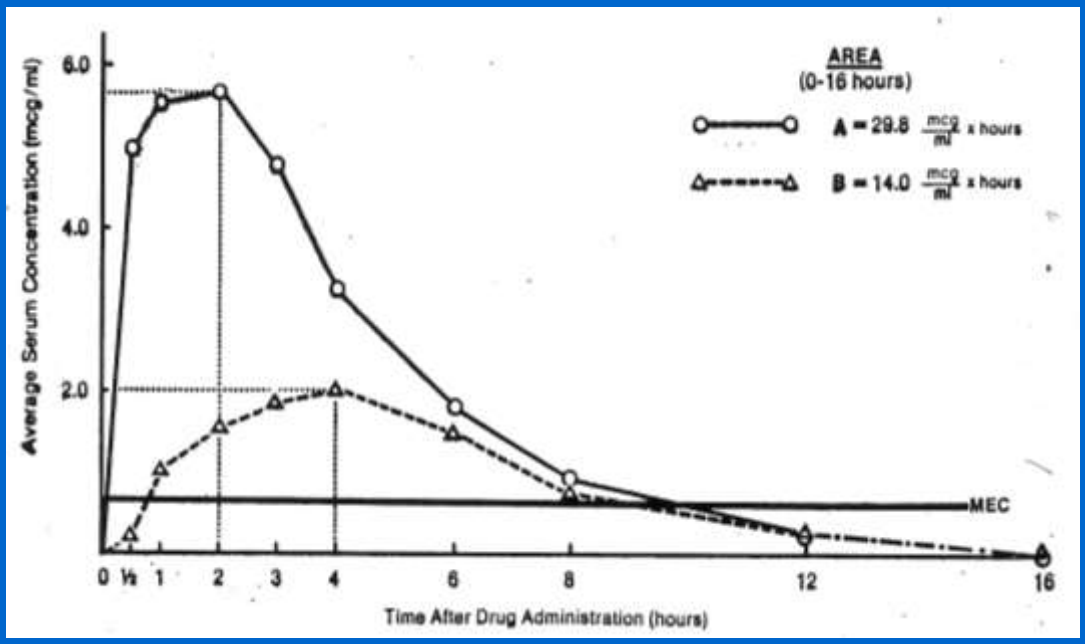
AUC A > B:
Therapeutic Significance?



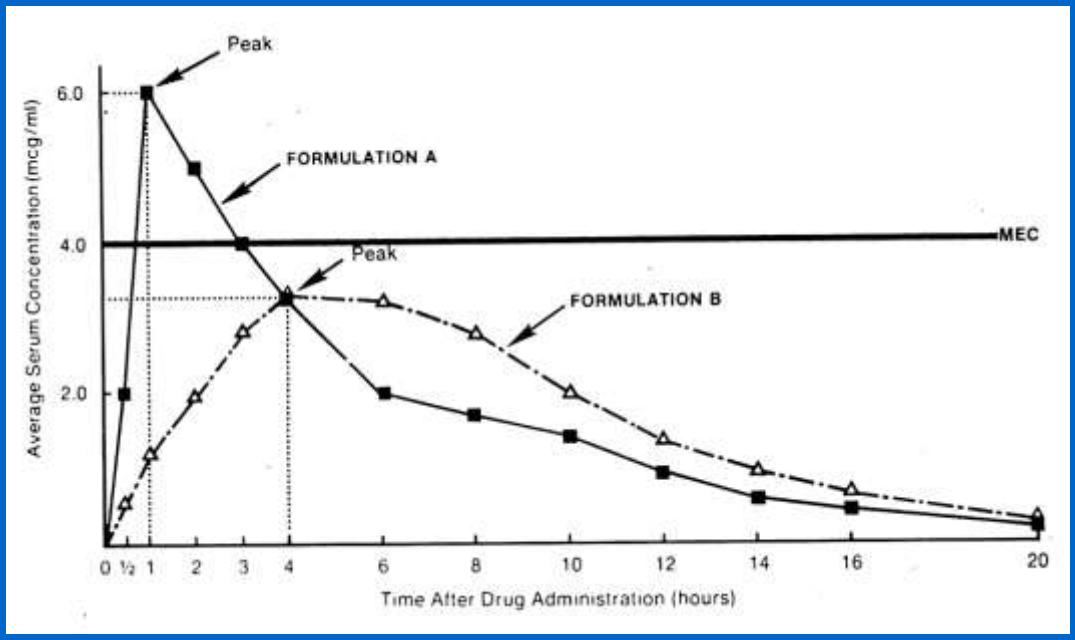
AUC A > B: B Ineffective



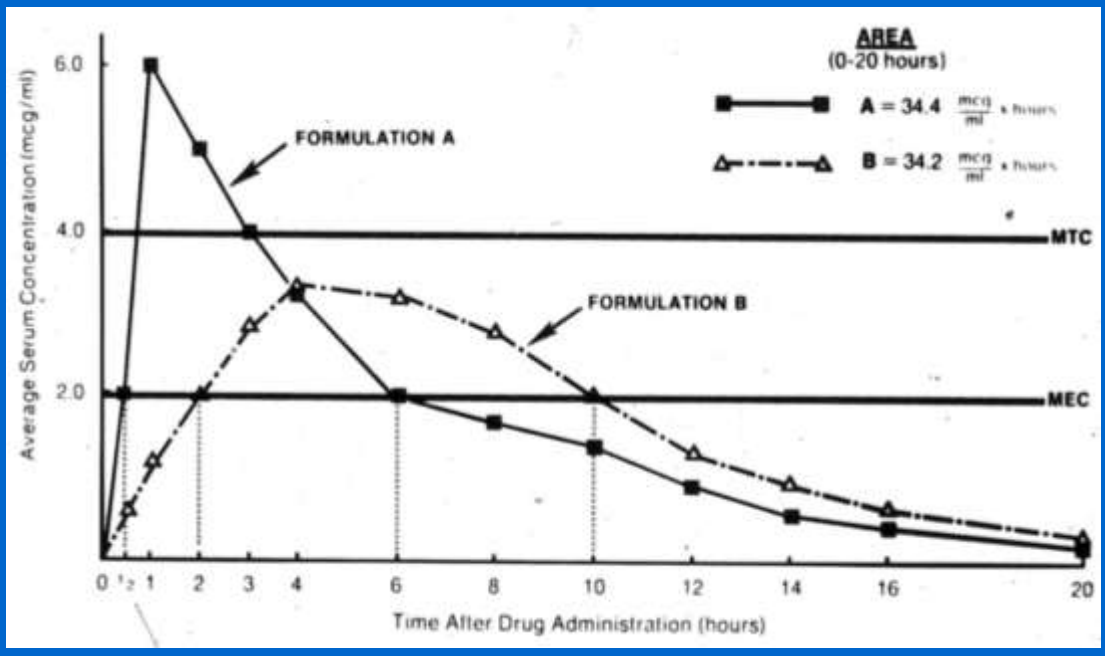
AUC A > B:
A and B Equally Effective



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

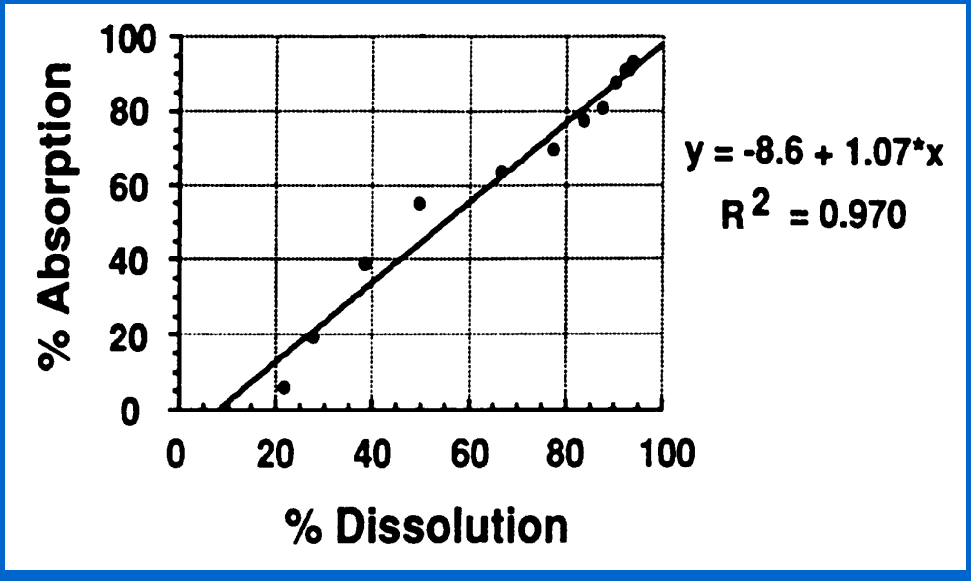
  GOOD = Highest Dose in 250 mL H_2O, pH 1.0-7.5

- **Dissolution Rate** of Formulation

  GOOD = 85% Dissolution in 15 min

- Intestinal **Permeability** of Drugs

CORRELATION of Rates of Drug *DISSOLUTION* and Oral *ABSORPTION*

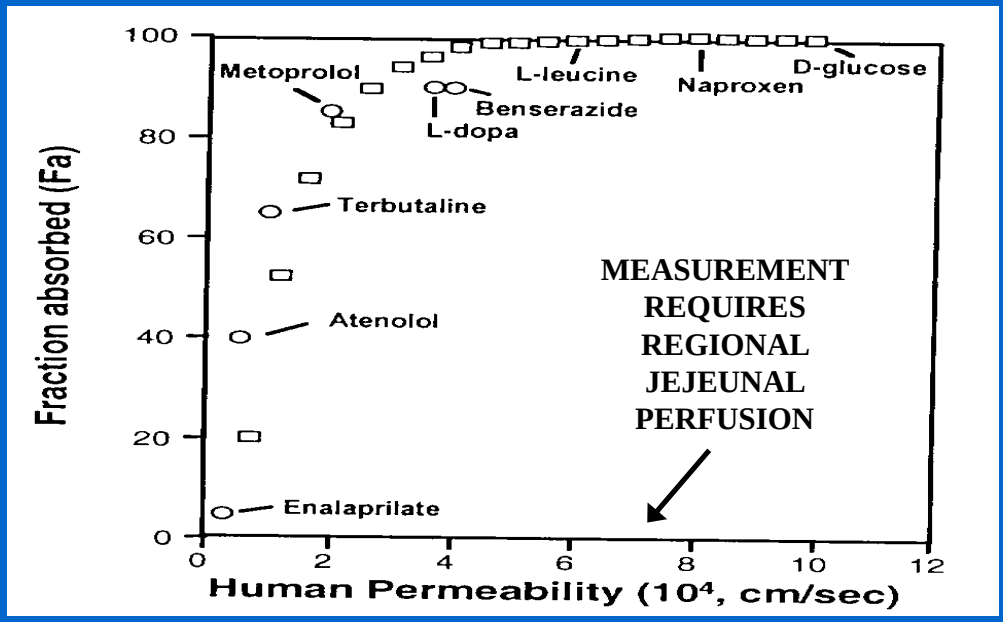


* From Rackley RJ. In Young D, Devane JG, Butler J, eds. In vitro-in vivo correlations. p. 1-15.

Three CRITICAL Biopharmaceutical Properties

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

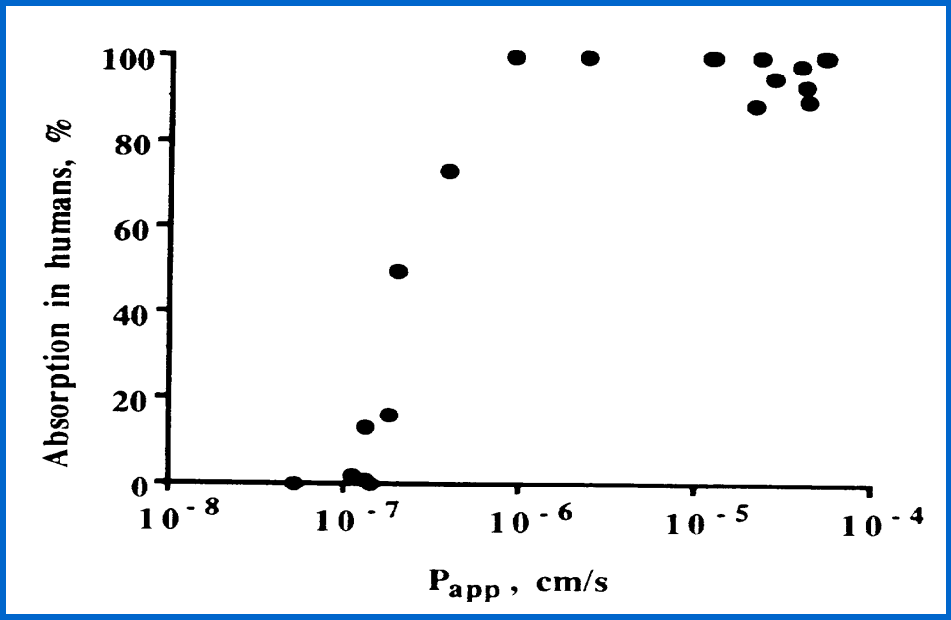
Bioavailability vs. *Jejeunal Permeability**



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

Bioavailability vs. *Caco-2 Cell Permeability*

P_{app}*



* 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.**