Factors

- pH, solubility, etc……
- Absorption Surface
- Dissolved concentration
- GI secretions, hydrolysis/ metabolism
- Bacterial metabolism
- GI motility
- Drug-drug interactions
- Disorders
- Shunts
- Food

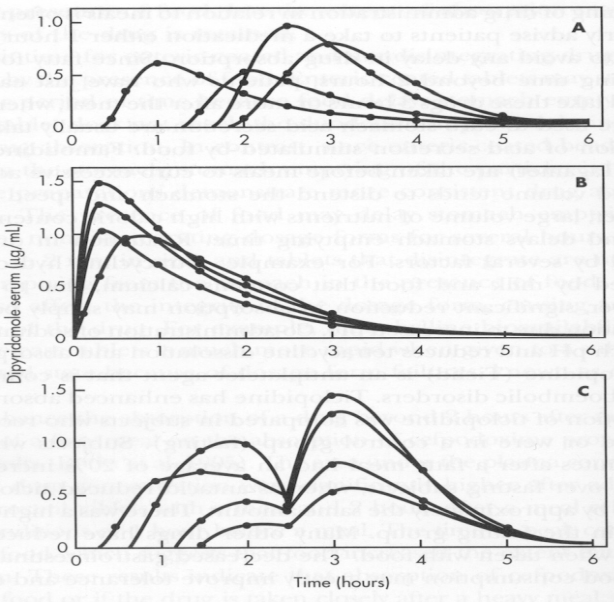
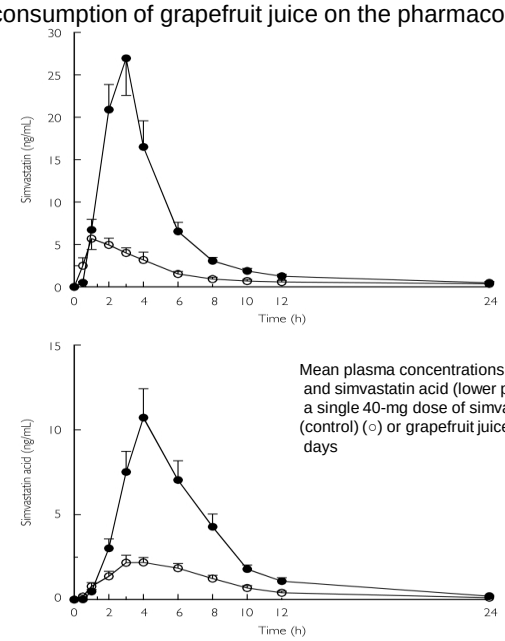


Figure 13-16. Serum concentrations of dipyridamole in three groups of four volunteers each. **A.** After taking 25 mg as tablet intact. **B.** As crushed tablet. **C.** As tablet intact 2 hours before lunch. (From Mellinger and Bohorfoush, 1966, with permission.)

Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin



Mean plasma concentrations of simvastatin (upper panel) and simvastatin acid (lower panel) after administration of a single 40-mg dose of simvastatin with 200 ml water (control) (○) or grapefruit juice (•) ingested once daily for 3 days

Lija *et al.* Br J Clin Pharmacol. 2004 July; 58(1): 56–60.

Factors Affecting Gut Absorption: Food and Nutrients II

- Vitamin B_{12}-Intrinsic factor complex is carried to the ileum, binds to a receptor. There is a separation and Vitamin B_{12} gets absorbed.
- Grapefruit juice can increase drug bioavailability:
  - inhibits the pre-systemic absorption of certain drugs (inhibits the intestinal efflux transporter P-glycoprotein)
  - inhibits certain cytochrome P450 enzymes (gut and/or liver) involved in metabolism

What's In a Name?

- Generic name (established non-proprietary common name of active ingredient): e.g. acetaminophen
- Chemical name (used by organic chemists; indicates structure): e.g. *p*-acetamidophenol (*p*-hydroxyacetaniline)
- Brand name (privately owned trade name of a drug): e.g. tylenol

Plasma Observations

- "Bioavailability" is a reference to the **rate** and **extent** to which a drug is absorbed.
- The F and k_a are direct measures of bioavailabilty but are too variable (recall why) to be useful for this purpose.
- From an oral C_p vrs t curve, the C_{max}, t_{max} and AUC are used (as indirect measures) to determine the bioavailability of a drug.
  - C_{max}, is a measure of **rate and extent** of absorption Ref Fig15-2
  - t_{max} is a measure of the **rate** of absorption
  - AUC is a measure of the **extent** of absorption Ref Fig 15-3 & 4

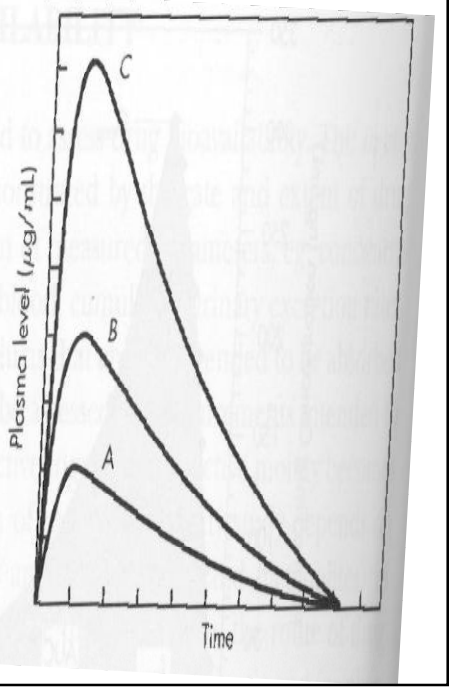


Figure 15-2. Plasma level–time curve following administration of single doses of **(A)** 250 mg, **(B)** 500 mg, and **(C)** 1000 mg of drug.

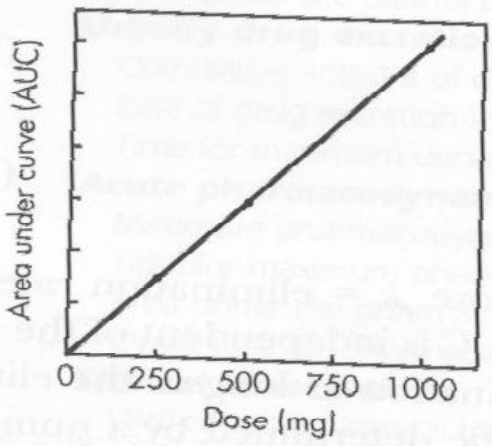


Figure 15-3. Linear relationship between AUC and dose (data from Fig. 15-2).

Urine Observations

- If absorption is greater for one drug product than another, then more of the first product should appear in the urine (for most drugs elimination is first order). Ref Fig 15-6 , 7 and 9
- Enough time should be allowed for the collection of the amount of absorbed drug in the urine (about five $t_{1/2}$s)
- A_U^∞ is the total amount of absorbed drug that is ultimately excreted unchanged
- A_U^∞ is a measure of the extent of drug absorption

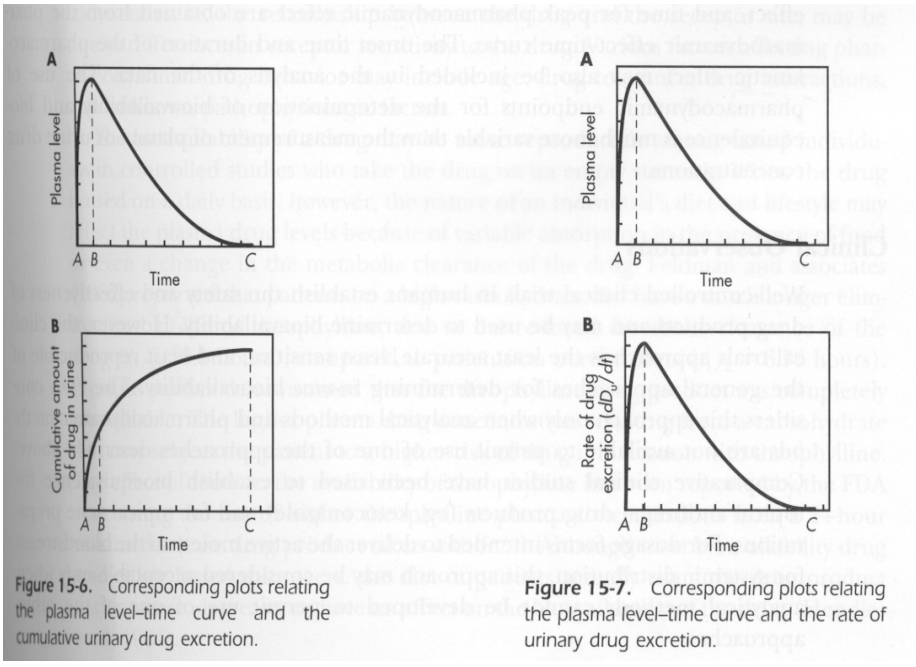


Figure 15-6. Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

Figure 15-7. Corresponding plots relating the plasma level–time curve and the rate of urinary drug excretion.

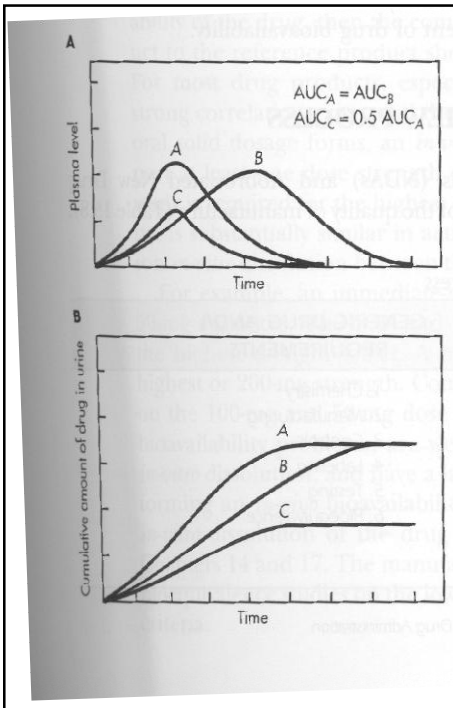


Figure 15-9. Corresponding plots relating plasma concentration and urinary excretion data.

Relative Bioavailability

- This compares the extent of absorption of a test product (generic drug) with a standard or reference product
- The systemic availability of a drug in a given drug product relative to its availability in a standard formulation (such as the Reference Listed Drug)
- For two products given at the same dose:

$$\textbf{Relative Bioavailability} = \frac{[\textbf{AUC}]_{\textbf{test}}}{[\textbf{AUC}]_{\textbf{reference}}}$$

OR

$$\textbf{Relative Bioavailability} = \frac{\textbf{D}_{\textbf{U}_{\textbf{test}}}^{\infty}}{\textbf{D}_{\textbf{U}_{\textbf{reference}}}^{\infty}}$$

Relative Bioavailability II

- If the doses are not the same,

$$\textbf{Relative Bioavailability} = \frac{[\text{AUC}]_{\text{test}}}{\text{dose}_{\text{test}}} \div \frac{[\text{AUC}]_{\text{reference}}}{\text{dose}_{\text{reference}}}$$

- Or,

$$\textbf{Relative Bioavailability} = \frac{[\text{AUC}]_{\text{test}}}{[\text{AUC}]_{\text{reference}}} \frac{\text{dose}_{\text{reference}}}{\text{dose}_{\text{test}}}$$

- A high relative bioavailability means two products may be considered bioequivalent. It does not necessarily mean that either product is well absorbed
- Ref Practice Problem on Page 407 (5th Edition Page 459)

Absolute Bioavailability

- This is a reference to the fraction of the oral dose (of an individual product) that is absorbed.
- For the same drug dose given po and iv:

$$\textbf{Absolute Bioavailability} = \frac{[\text{AUC}]_{\text{oral}}}{[\text{AUC}]_{\text{iv}}}$$

OR

If the doses are different:

$$\textbf{Absolute Bioavailability} = \frac{[\text{AUC}]_{\text{oral}}}{[\text{AUC}]_{\text{iv}}} \frac{\text{dose}_{\text{iv}}}{\text{dose}_{\text{oral}}}$$

Bioavailability Studies Rationale

- These contribute to assure that standards of safety and effectiveness of a drug (identity, strength, purity etc..) are met.
- For new generic products (as well as new formulations of old drugs) FDA requires *in vitro* and/or *in vivo* studies of bioavailability along with essential pharmacokinetic parameters (such as $t_{1/2}$, rates of absorption, excretion and metabolism) are met.
- Data from bioavailability studies help determine appropriate dose regimens

Bioequivalence

- *Bioequivalent drug products* show similar bioavailability when studied under similar conditions
- Bioequivalence is demonstrated by establishing that no *statistical difference* exists among C_{max}, t_{max} and AUC for the test and reference products
- Analysis of Variance (ANOVA) is a commonly used test (level of probability of < 0.05 and a power of 80% certainty). The average parameter value of the test product should be *within 20%* of that of the reference product

Bioequivalence II

- FDA: “The **rate** and **extent** of absorption of the test drug **do not show a significant difference** from the rate and extent of absorption of the reference drug when administered at the same molar dose of therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses”
- Or: where there is **no difference in the extent** of absorption but a **significant difference in the rate** of absorption that is intentional, reflected in the label and is medically insignificant

Bioequivalence Studies

- Ref Table 15-1
- Typically single-dose (usually following an overnight fast), two-treatment, randomized cross over design. Plasma sample taken just before dose and at regular intervals thereafter. Food intervention studies and multiple-dose studies are sometimes performed

TABLE 15.1 Methods for Assessing Bioavailability and Bioequivalence

Plasma drug concentration
Time for peak plasma (blood) concentration (t_{max})
Peak plasma drug concentration (C_{max})
Area under the plasma drug concentration–time curve (AUC)
Urinary drug excretion
Cumulative amount of drug excreted in the urine (D_u)
Rate of drug excretion in the urine (dD_u/dt)
Time for maximum urinary excretion (t)
Acute pharmacodynamic effect
Maximum pharmacodynamic effect (E_{max})
Time for maximum pharmacodynamic effect
Area under the pharmacodynamic effect–time curve
Onset time for pharmacodynamic effect
Clinical observations
Well-controlled clinical trials
***In-vitro* studies**
Drug dissolution

Bioequivalence Studies II

- Latin square. Each subject receives each drug product only once, with sufficient time between product administrations to allow for : 1. full description of C_{max}, t_{max} and AUC and 2. elimination of product from the body Ref Table 15.3 &4
- Replicated crossover design: estimates within-subject variance for both products. FDA recommends a four-period, two-sequence, two-formulation design

TABLE 15.3 Latin-Square Crossover Design for a Bioequivalence Study of Three Drug Products in Six Human Volunteers

	DRUG PRODUCT		
SUBJECT	Study Period 1	Study Period 2	Study Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

TABLE 15.4 Latin-Square Crossover Design for a Bioequivalency Study of Four Drug Products in 16 Human Volunteers

	DRUG PRODUCT			
SUBJECT	Study Period 1	Study Period 2	Study Period 3	Study Period 4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C
5	A	B	D	C
6	B	D	C	A
7	D	C	A	B
8	C	A	B	D
9	A	C	B	D
10	C	B	D	A
11	B	D	A	C
12	D	A	C	B
13	A	C	D	B
14	C	D	B	A
15	D	B	A	C
16	B	A	C	D

Generic Substitution

- Generic Substitution: Dispensing an unbranded product or a different brand in place of a prescribed product.
- Same dosage form, same active ingredient, different manufacturer.
- If permitted by prescriber
- The FDA publishes a list of drug products: *Approved Drug Products with Therapeutic Equivalence Evaluations,* also known as the Orange Book.
- Overall classification: A (deemed therapeutically equivalent) or B (inadequate evidence of bioequivalence)
- Two-letter codes used
- Ref Table 15.14

TABLE 15.14 Therapeutic Equivalence Evaluation Codes

A Codes

Drug products considered to be therapeutically equivalent to other pharmaceutically equivalent products

- AA Products in conventional dosage forms not presenting bioequivalence problems
- AB Products meeting bioequivalence requirements
- AN Solutions and powders for aerosolization
- AO Injectable oil solutions
- AP Injectable aqueous solutions
- AT Topical products

B Codes

Drug products that the FDA does not consider to be therapeutically equivalent to other pharmaceutically equivalent products

- B* Drug products requiring further FDA investigation and review to determine therapeutic equivalence
- BC Extended-release tablets, extended-release capsules, and extended-release injectables
- BD Active ingredients and dosage forms with documented bioequivalence problems
- BE Delayed-release oral dosage forms
- BN Products in aerosol–nebulizer drug delivery systems
- BP Active ingredients and dosage forms with potential bioequivalence problems
- BR Suppositories or enemas for systemic use
- BS Products having drug standard deficiencies
- BT Topical products with bioequivalence issues
- BX Insufficient data

Adopted from: *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) (www.fda.cder/ob/default.htm) 2003.

Pharmaceutical Substitution

- Pharmaceutical Alternatives: same therapeutic entity but presented as different salts, complexes or esters. Also different dosage forms (e.g. elixirs, capsules and tablets) and strengths by a single manufacturer.
- Pharmaceutical Equivalents: same active ingredient, same amount of it, same dosage form for the same route of administration. Must meet same uniformity, disintegration and dissolution rates where applicable. May differ in features such as packaging, shape, color, release mechanism, excipients and some labeling details
- The process of dispensing a *pharmaceutical alternatives* in place of a prescribed product.
- Needs prescriber approval

Therapeutic Substitution

- Therapeutic alternatives: different active ingredients share same indications and used for same therapeutic objectives e.g. ibuprofen instead of ASA
- Therapeutic equivalents: are pharmaceutic equivalents that are expected to have the same clinical effect and safety profile
- Therapeutic substitution involves the use of a therapeutic alternative

Drug Review Process

- Contrast New Drug Applications (NDAs) and Abbreviated New drug Applications (ANDAs) Ref Table 15.8
- NDAs must have animal and clinical data along with *bioavailablity* data.
- ANDAs do not need these but must have bioequivalence data Fig 15-10

Biopharmaceutics Classification System

- Used to predict in vivo absorption based on **solubility** and **permeability** characteristics Ref Table 15.11
- $J_w = P_w C_w$
- J_w= drug flux (mass/area/time), P_w=permeability of membrane, C_w= drug concentration at intestinal membrane surface