Bioavailability and Bioequivalence

Pharmacokinetics of Drug Absorption

- The systemic drug absorption from the gastrointestinal (GI) tract or from any other extravascular site is dependent on:

1) **The physicochemical properties of the drug.**
2) **The dosage form used.**
3) **The anatomy and physiology of the absorption site.**

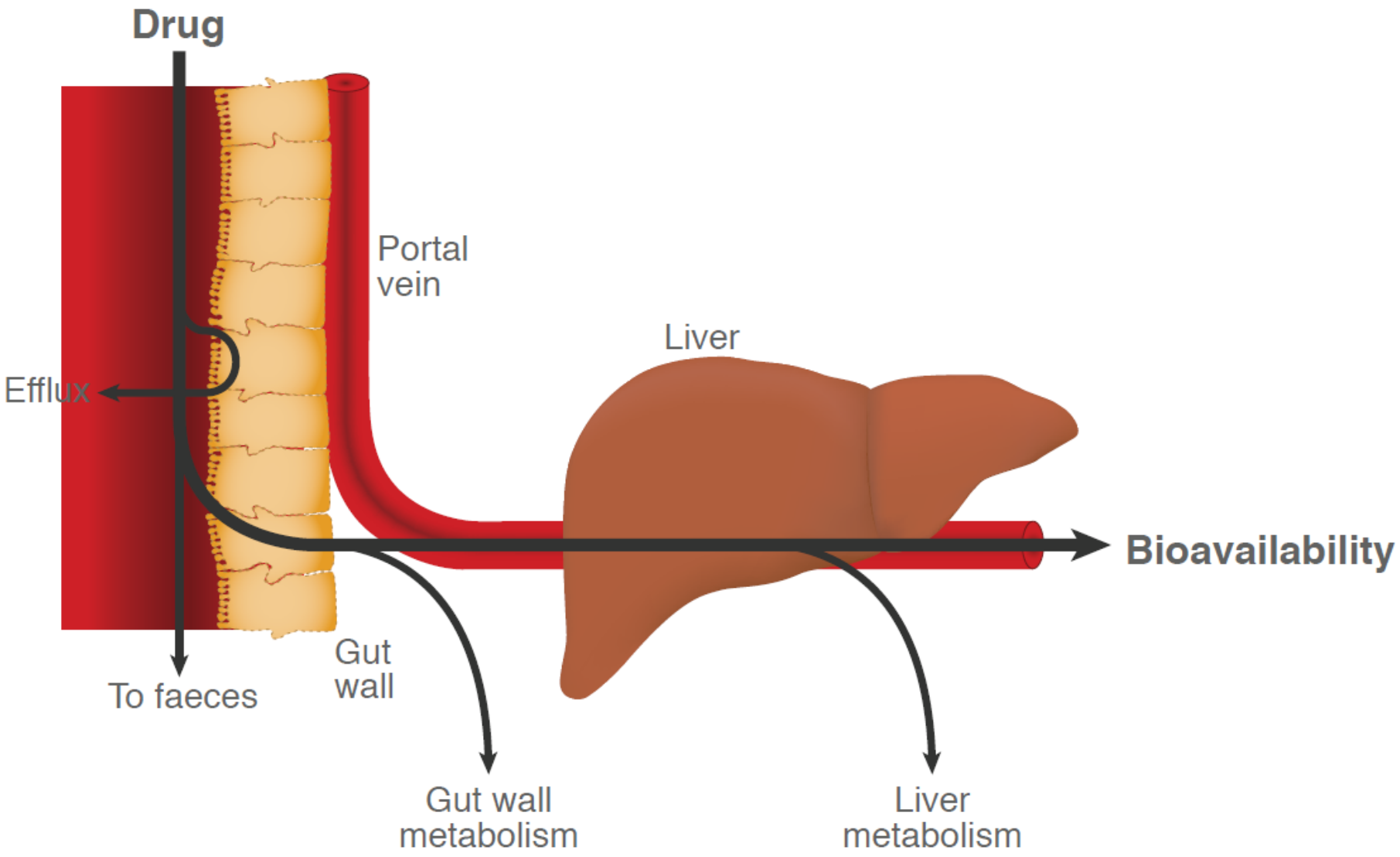
Factors Affecting Absorption

- Formulation factors
  - Tablet disintegration
  - Inert ingredient / solvent effects
  - Solubility
  - Drug pka
  - Concentration
- Patient factors
  - Absorbing surface
  - Blood flow
  - pH
  - GI motility
  - Disease states
  - Interactions with food,

GI Physiology and Drug Absorption

	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
BUCCAL	approx 7	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
ESOPHAGUS	5 - 6	Very thick, no absorption	-	small	short	-
STOMACH	1 - 3 decomposition, weak acid unionized	normal	good	small	30 - 40 minutes, reduced absorption	no
DUODENUM	6 - 6.5 bile duct, surfactant properties	normal	good	very large	very short (6" long), window effect	no
SMALL INTESTINE	7 - 8	normal	good	very large 10 - 14 ft, 80 cm^2 /cm	about 3 hours	no
LARGE INTESTINE	5.5 - 7	-	good	not very large 4 - 5 ft	long, up to 24 hr	rectum yes

Figure 3.1: Schematic illustrating First Pass Metabolism by the Gut Wall and the Liver prior to Reaching the Systemic Circulation.



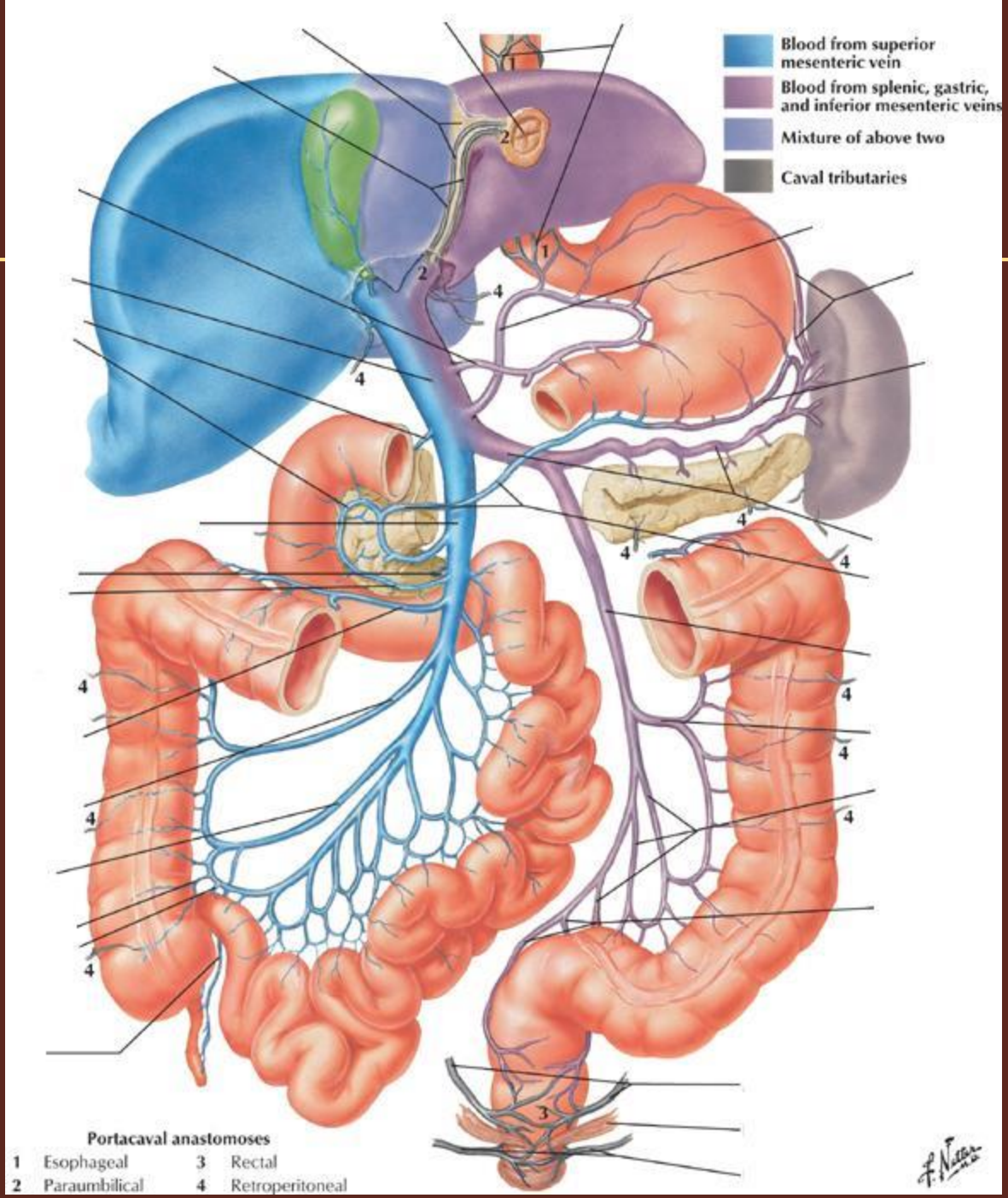
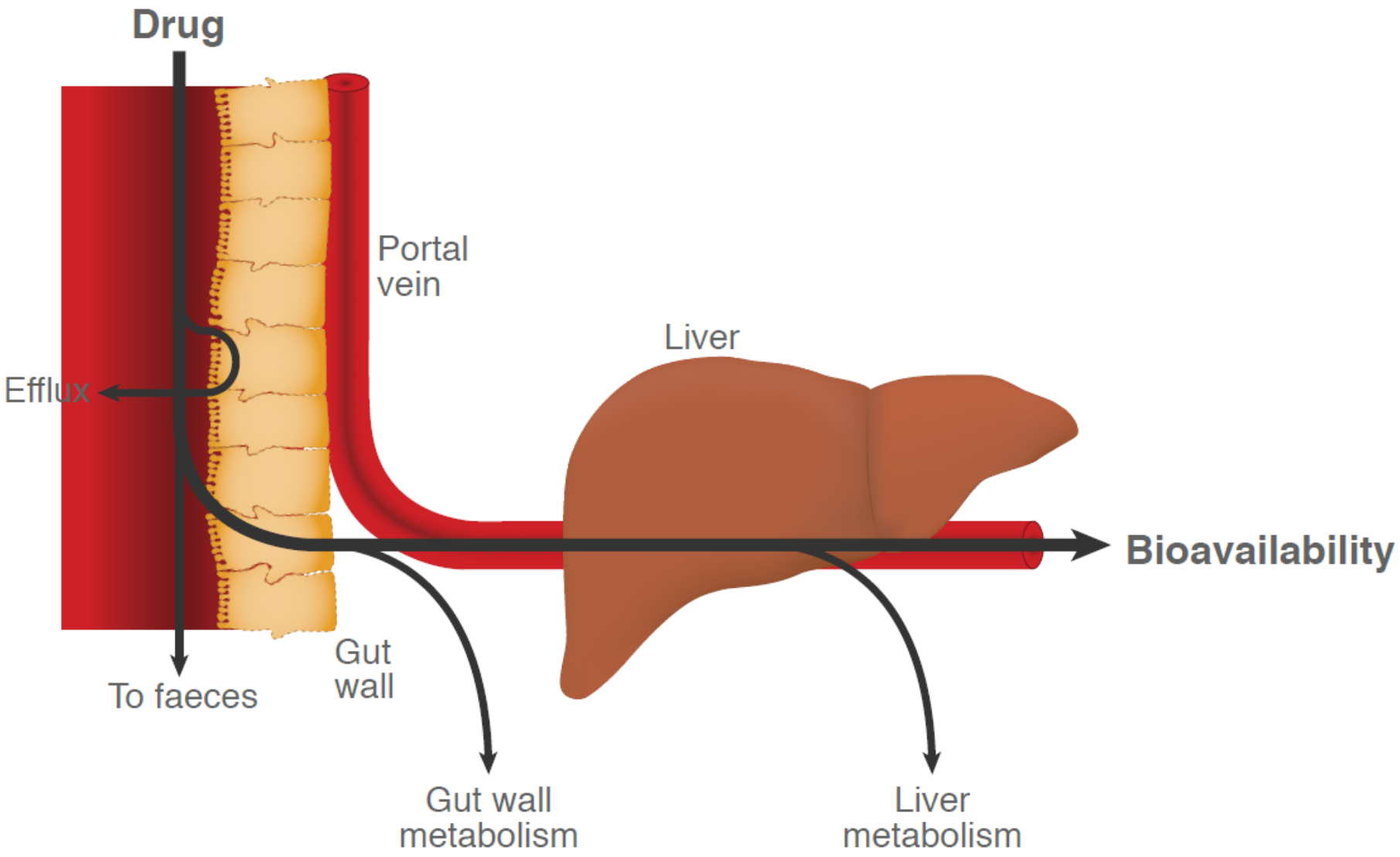
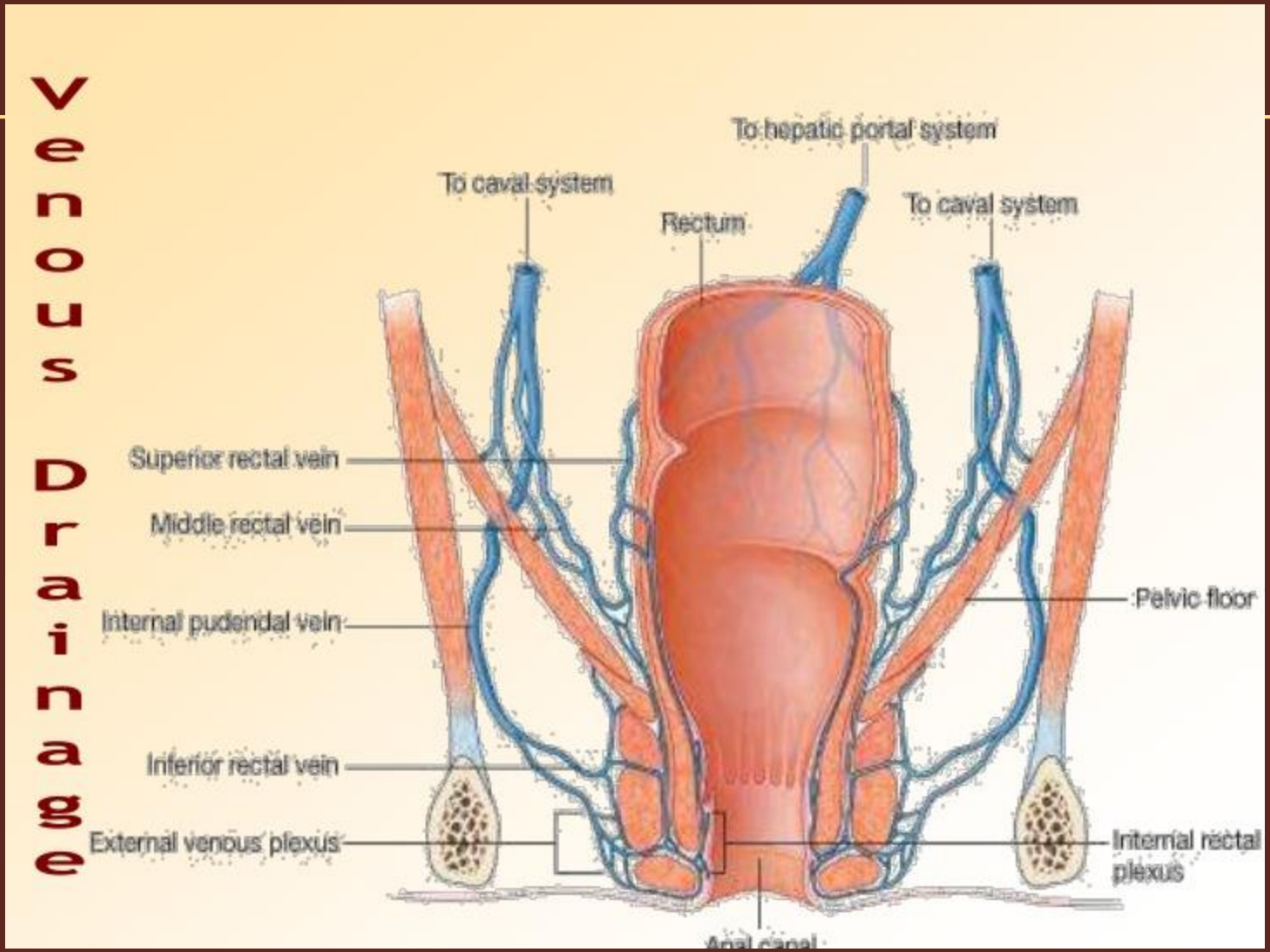

Blood from superior mesenteric vein
Blood from splenic, gastric, and inferior mesenteric veins
Mixture of above two
Caval tributaries
Portacaval anastomoses
1 Esophageal
2 Paraumbilical
3 Rectal
4 Retroperitoneal

Figure 3.1: Schematic illustrating First Pass Metabolism by the Gut Wall and the Liver prior to Reaching the Systemic Circulation.



Venous Drainage



Gastric emptying and motility

- Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore increasing stomach emptying will increase drug absorption.
- The quicker the stomach emptying the higher the plasma concentration.
- Also slow stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

Food

- Food can effect the rate of gastric emptying.
- For example fatty food can slow gastric emptying and retard drug absorption. Generally the extent of absorption is not greatly reduced.
- Occasionally absorption may be improved. Griseofulvin absorption is improved by the presence of fatty food. Apparently the poorly soluble griseofulvin is dissolved in the fat and then more readily absorbed.

The Effect of Food on the Bioavailability of Selected Drugs

- https://accesspharmacy.mhmedical.com/ViewLarge.aspx?figid=100672865&gbosContainerID=null&gbosid=null&groupID=null

Routes of Drug Administration

- The route of administration (ROA) that is chosen may have a profound effect upon the speed and efficiency with which the drug acts.
- Appropriate administration route depends on:
  - ✓ the dosage form in which the drug is available
  - ✓ the patient's age
  - ✓ the patient's condition, e.g. level of consciousness

TABLE 14-1 Common Routes of Drug Administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume. Insulin formulaton can vary from short to intermediate and long acting

			short to intermediate and long acting.
Intradermal injection	Drug injected into surface area (dermal) of skin.	Often used for allergy and other diagnostic tests, such as tuberculosis.	Some discomfort at site of injection.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending on muscle group injected and blood flow.
Intra-arterial injection	100% of solution is absorbed.	Used in chemotherapy to target drug to organ.	Drug may also distribute to other tissues and organs in the body.
Intrathecal Injection	100% of solution is absorbed.	Drug is directly injected into cerebrospinal fluid (CSF) for uptake into brain.	

TABLE 14-1 Common Routes of Drug Administration (Continued)

Route	Bioavailability	Advantages	Disadvantages
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.	Used more in small laboratory animals. Less common injection in humans. Used for renally impaired patients on peritoneal dialysis who develop peritonitis.	Drug absorption via mesenteric veins to liver, may have some hepatic clearance prior to systemic absorption.
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipidsoluble drugs.	No "first-pass" effects. Buccal route may be formulated for local prolonged action. Eg, adhere to the buccal mucosa with some antifungal. Buccal is different from sublingual which is usually placed "under tongue."	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Enteral Routes			
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.

Other Routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW (molecular weight).	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

- **Rapid Gastric Emptying Advisable when :**
  - Rapid onset of action is desired eg. Sedatives

  - Dissolution occurs in the intestine eg. Enteric coated tablets
  - Drugs not stable in GI fluids eg. penicillin G
  - Drug is best absorbed from small intestine eg. Vitamin B_{12}
- **Delay in Gastric Emptying recommended when**
  - Food promotes drug dissolution and absorption e.g. Gresiofulvin
  - Disintegration and dissolution is promoted by gastric fluids

Factors affecting Gastric Emptying

Volume of Ingested Material	Bulky material tends to empty more slowly than liquids
Type of Meal	Gastric emptying rate: carbohydrates > proteins > fats
Temperature of Food	Increase in temperature, increase in emptying rate
Body Position	Lying on the left side decreases emptying rate and right side promotes it
GIT pH	Retarded at low stomach pH and promoted at higher alkaline pH
Emotional state	Anxiety and stress promotes where as depression retards it
Disease states	gastric ulcer, diabetes and hypothyroidism retards it, while duodenal ulcer, hyperthyroidism promotes it.

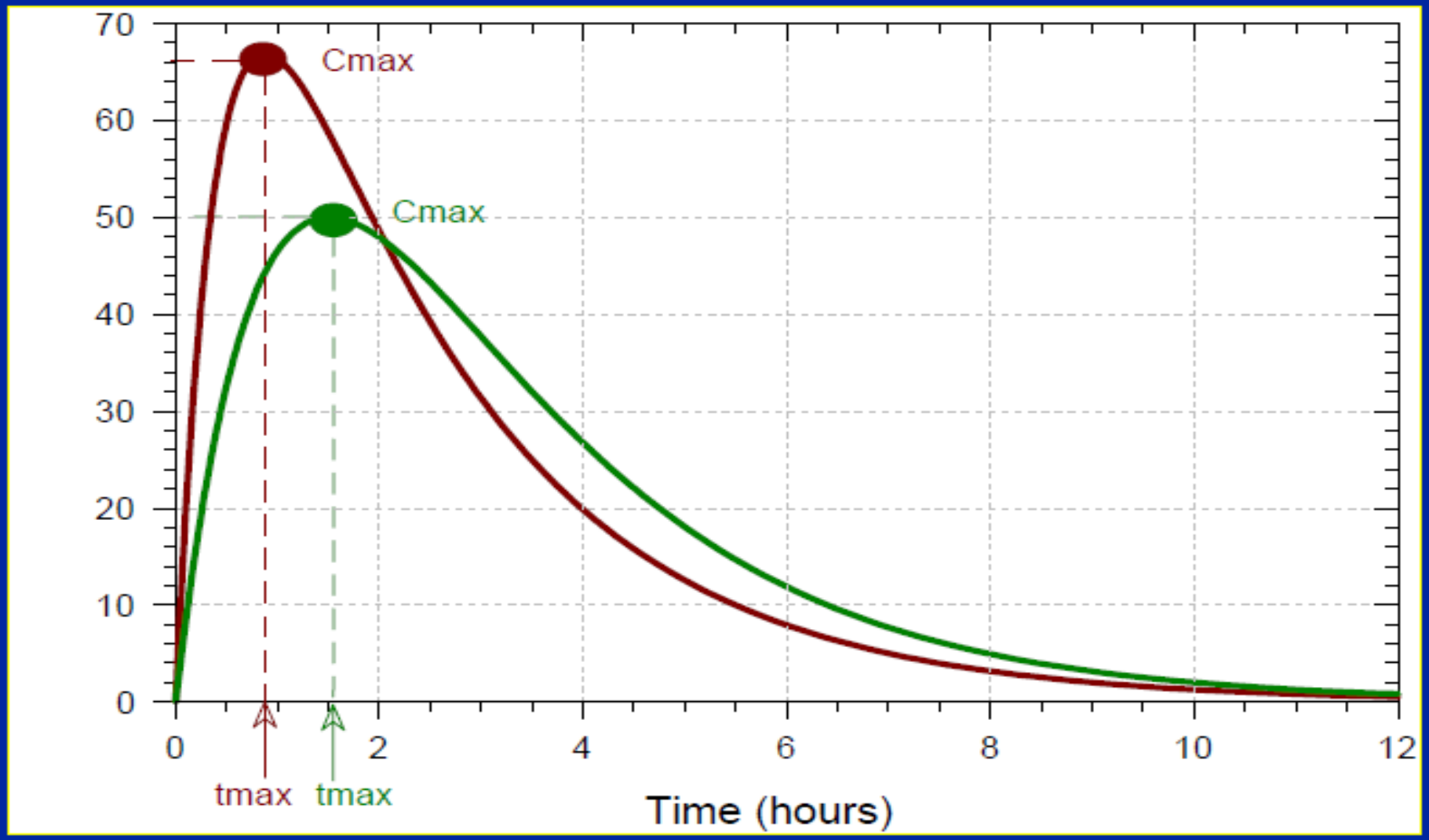
Bioavailability

- Bioavailability is a measurement of the rate and extent (amount) to which the active ingredient or active moiety becomes available at the site of action.

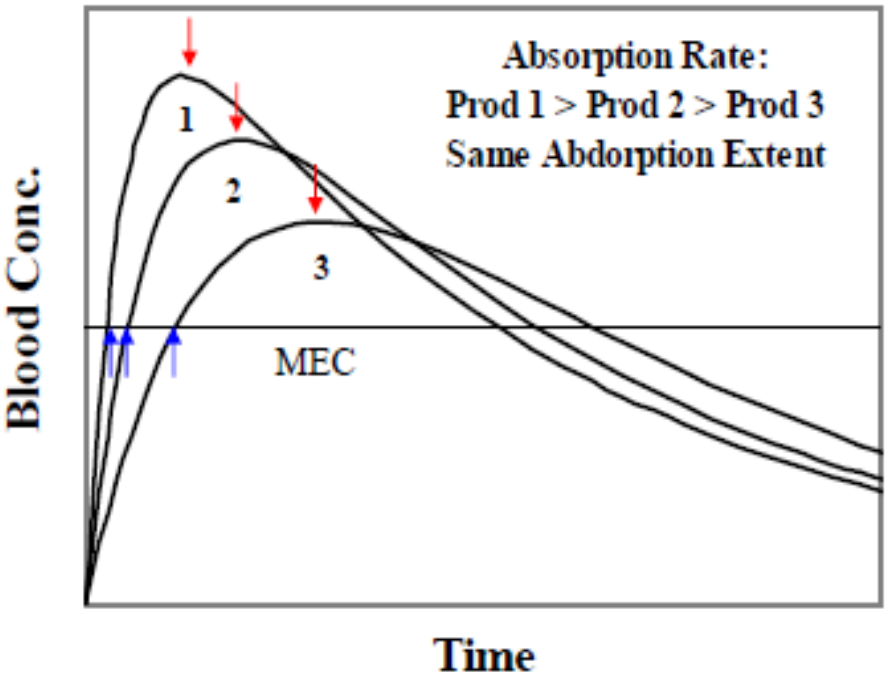
- Bioavailability is also considered as a measure of the rate and extent of therapeutically active drug that is systemically absorbed.

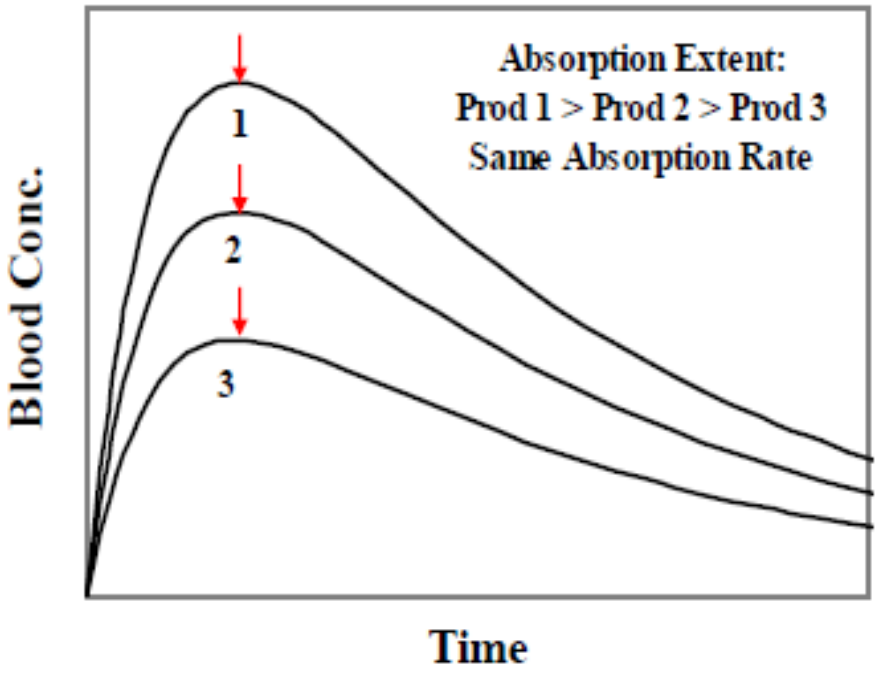
Bioavailability

Rate and Extent of Absorption



Bioavailability – Rate and Extent of Drug Absorption into the Systemic Circulation

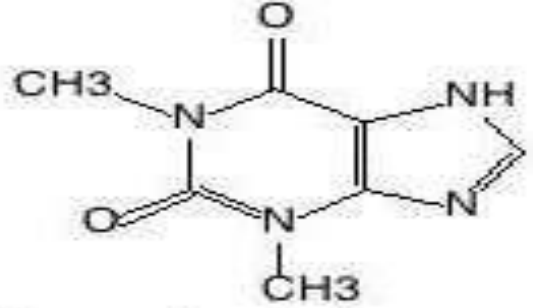




- Rate of drug absorption mainly affects the time to onset of action (↑), as well as timing and magnitude of maximal effect (↑).
- Extent of absorption affects maximal effect and overall exposure as measured by area under the blood concentration-time curve (AUC).

Definitions

- **Brand Name:** is the trade name of the drug.
- **Chemical Name:** is the name used by the organic chemist to indicate the chemical structure of the drug.
- **Drug Product** means a finished dosage form, e.g., tablet, capsule, or solution, that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.
- **Generic Name** is the established, non proprietary or common name of the active drug in a drug product.



Chemical Structure

$C_7H_8N_4O_2$
Molecular Formula

180.17
Molecular Weight

3,7-dihydro-1,3-dimethyl-
1 H-purine-2,6-dione
Chemical Name

5967-84-0
CAS Number

Theophylline

Generic Name
US Approved Name

Brand Names

Tablet	Elixir	Capsule
Theo-Dur (Key)	Aerolate (Fleming)	Theospan (Laser)
Durapyl (McNeil)		Theobid (Glaxo)

A Collection of Names for the Same

Brand Drugs & Generic Drugs

- For generic products to be registered , a report of bioequivalent studies must be submitted to FDA.
- These bioequivalent studies must be done by independent centers which study generic product on healthy volunteers.

Brand Drugs & Generic Drugs

- Finally report if the generic product is accepted or rejected.
- According to report results FDA will register the drug to be marketed or reject it.
- If the drug is originator product, then the company must submit bioavailability studies (not bioequivalent) in addition to pharmacological profile, toxicological profile, preclinical studies, clinical studies,…

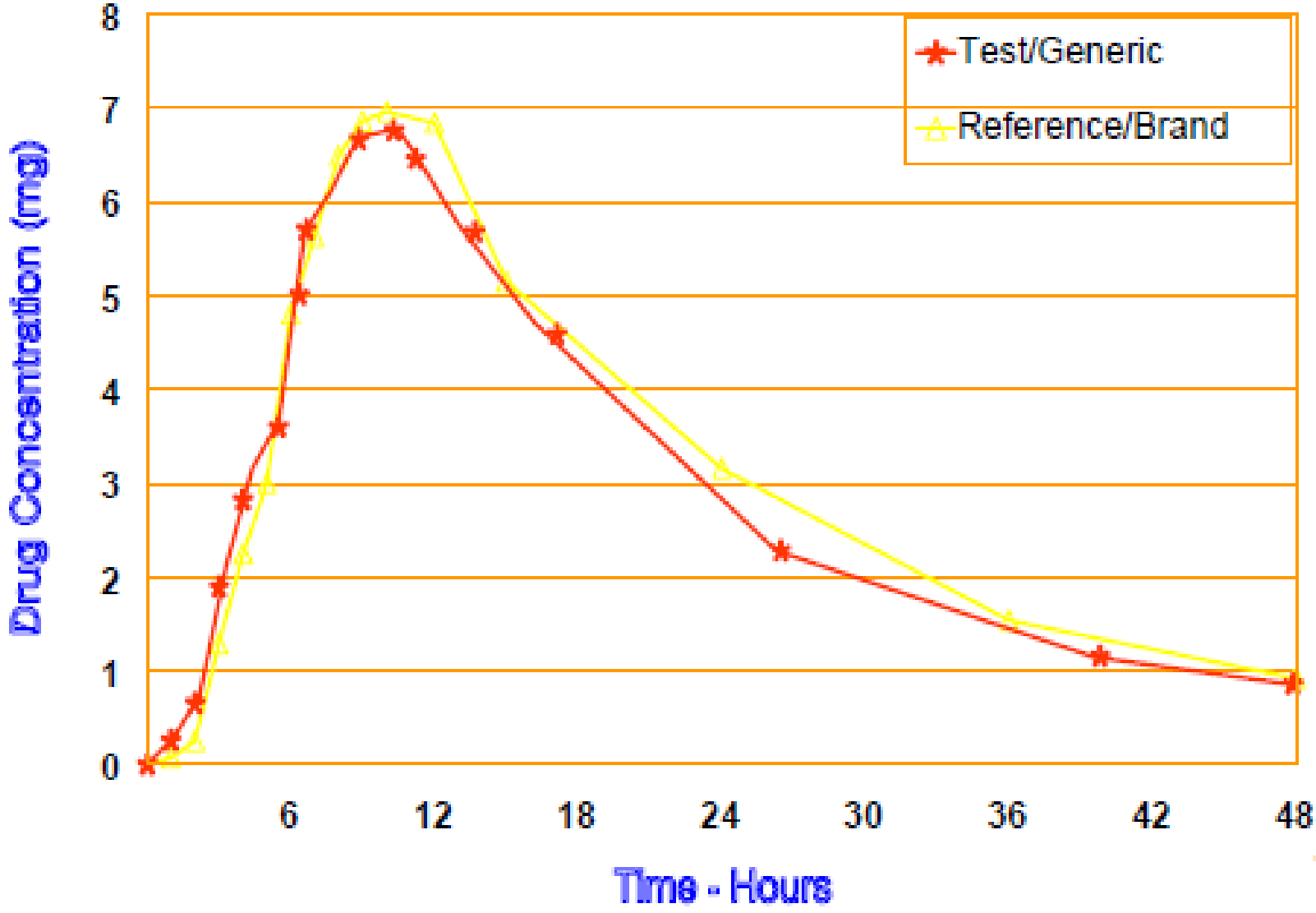
Brand Drugs & Generic Drugs

- Inventing new drugs is very difficult and time consuming process.
- Company may need 10-15 years for originator drug to be invented and marketed.
- For generic products, there is no need for pharmacological profile, toxicological profile, clinical studies,…
- However, there must be studies about bioequivalence and stability of finished product with similar shelf life.

Bioequivalent drug products

- A generic drug product is considered bioequivalent to the Reference (generally the brand name) drug product if both products are pharmaceutical equivalents or pharmaceutical alternatives and its rate and extent of systemic drug absorption (bioavailability) do not show a statistically significant difference when administered:
  - in the same dose of the active ingredient.
  - in the same chemical form.
  - in a similar dosage form.
  - by the same route of administration.
  - under the same experimental conditions.

Bioequivalence



Generic drug product

- The generic drug product requires an Abbreviated New Drug Application (**ANDA**) for approval by the United States Food and Drug Administration (**FDA**) and may be marketed after patent expiration of the Reference drug product.

- The Reference drug product is usually the currently marketed, brand name product with a full New Drug Application (**NDA**) approved by the FDA.

Generic drug product

- The generic drug product must be a therapeutic equivalent to the Reference drug product but may differ in certain characteristics including shape, scoring configuration, packaging, and excipients (including colors, flavors, preservatives, expiration date, and minor aspects of labeling).

Pharmaceutical Equivalents

- Pharmaceutical equivalents are drug products that contain:
  - **The same therapeutically active drug ingredient(s), same salt, ester, or chemical form.**
  - **The same dosage form.**
  - **Are identical in strength and concentration and route of administration.**

Pharmaceutical Equivalents

- Pharmaceutical equivalents may differ in characteristics such as:
  - **Shape.**
  - **Scoring configuration.**
  - **Release mechanisms.**
  - **Packaging.**
  - **Excipients (including colors, flavoring, preservatives).**

Therapeutic equivalent drug products

- Therapeutic equivalent drug products are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when administered to patients under the same conditions specified in the labeling.

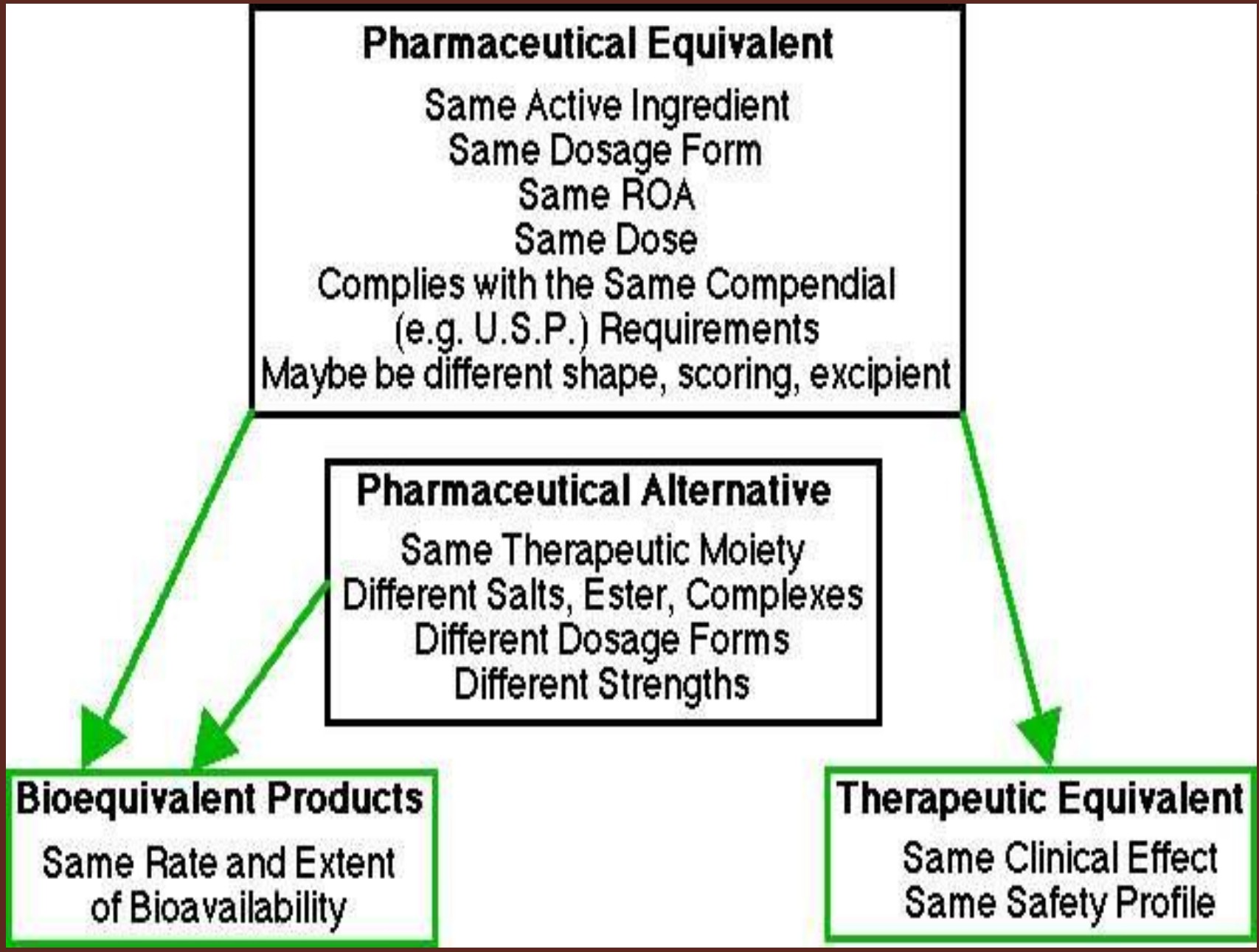
Therapeutic equivalent drug products

- Therapeutic equivalent drug products have the following criteria:

1) The products are safe and effective.
2) The products are pharmaceutical equivalents containing the same active drug ingredient in the same dosage form, given by the same route of administration, meet compendial or other applicable standards of strength, quality, purity, and identity, and meet an acceptable *in vitro* standard.

Pharmaceutical alternatives

- Pharmaceutical alternatives are drug products that contain the same therapeutic moiety but are different:
  - **Salts, esters, or complexes** (e.g., tetracycline hydrochloride versus tetracycline phosphate).
  - **Dosage forms** (e.g., tablet versus capsule; immediate release dosage form versus controlled release dosage form).
  - **Strengths.**



Summary of Bioavailability Definitions

Methods for Assessing Bioavailability and Bioequivalence

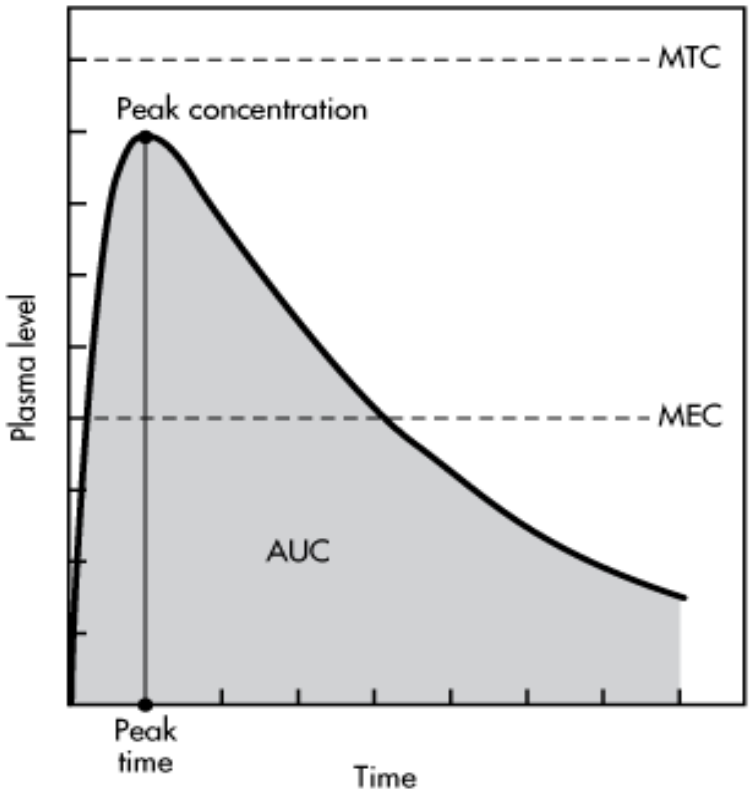
- BIOAVAILABILITY AND BIOEQUIVALENCE may be determined directly using:
  - **Plasma drug concentration verses time profiles.**
  - **Urinary drug excretion studies.**
  - **Measurements of an acute pharmacological effect.**
  - **Clinical studies.**
  - ***In vitro* studies.**

Acute pharmacologic effects

- Acute pharmacologic effects, such as changes in heart rate, blood pressure, electrocardiogram (ECG), clotting time can be used to measure bioavailability when:
  - No assay for plasma drug concentration is available.
  - The plasma drug concentration does not relate to the pharmacological response (e.g., a bronchodilator such as albuterol given by inhalation).

Plasma drug concentration

- The plasma drug concentration versus time curve is most often used to measure the systemic bioavailability of a drug from a drug product.



Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

Plasma drug concentration

- Time for peak plasma drug concentration (T_{max}) relates to the rate constants for systemic drug absorption and elimination.

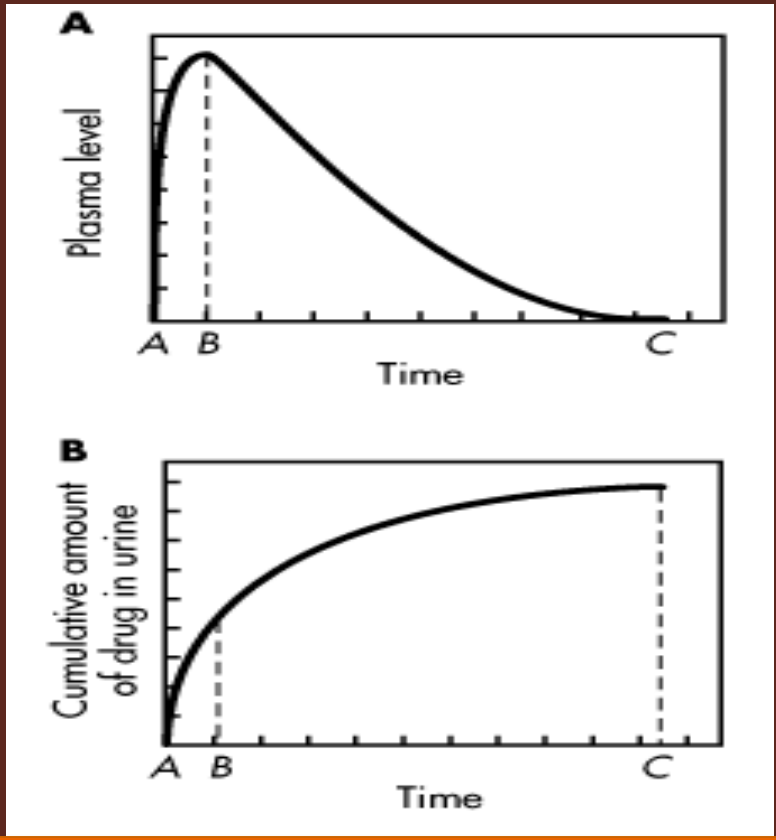
- If two oral drug products contain the same amount of active drug but different excipients, the dosage form that yields the faster rate of drug absorption has the shorter T_{max} because the elimination rate constant for the drug from both dosage forms is the same.

Plasma drug concentration

- Peak plasma drug concentration (C_{max}).
- The plasma drug concentration at T_{max} relates to the intensity of the pharmacological response. Ideally, C_{max} should be within the therapeutic window.
- Area under the plasma drug concentration versus time curve (AUC) relates to the amount or extent of drug absorption.
- The amount of systemic drug absorption is directly related to the AUC.

Urinary drug excretion

- Measurement of urinary drug excretion can determine bioavailability from a drug product.
- This method is most accurate if the active therapeutic moiety is excreted unchanged in significant quantity in the urine.



Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

Urinary drug excretion

- The cumulative amount of active drug excreted in the urine (D_u^{∞}) is directly related to the extent of systemic drug absorption.
- The rate of drug excretion in the urine (dD_u/dt) is directly related to the rate of systemic drug absorption.
- The time for the drug to be completely excreted (t^{∞}) corresponds to the total time for the drug to be systemically absorbed and completely excreted after administration.

Clinical studies

- Clinical (pharmacodynamic) responses to a drug can be used to measure bioavailability quantitatively.
- They are less precise than other methods and are highly variable because of individual differences in drug pharmacodynamics and subjective measurements.

In vitro studies

- Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data.

- For example, the rate of drug dissolution *in vitro* for certain drug products correlates with drug bioavailability *in vivo.*

In vitro studies

- If the dissolution test *in vitro* is considered statistically adequate to predict drug bioavailability, then dissolution may be used in place of an *in vivo* bioavailability study.

RELATIVE AND ABSOLUTE BIOAVAILABILITY

- Relative bioavailability is the systemic availability of the drug from a dosage form as compared to a Reference standard given by the same route of administration.

- Relative bioavailability is calculated as the ratio of the AUC for the dosage form to the AUC for the Reference dosage form given in the same dose.

RELATIVE AND ABSOLUTE BIOAVAILABILITY

- A relative bioavailability of 1 (or 100%) implies that drug bioavailability from both dosage forms is the same but does not indicate the completeness of systemic drug absorption.

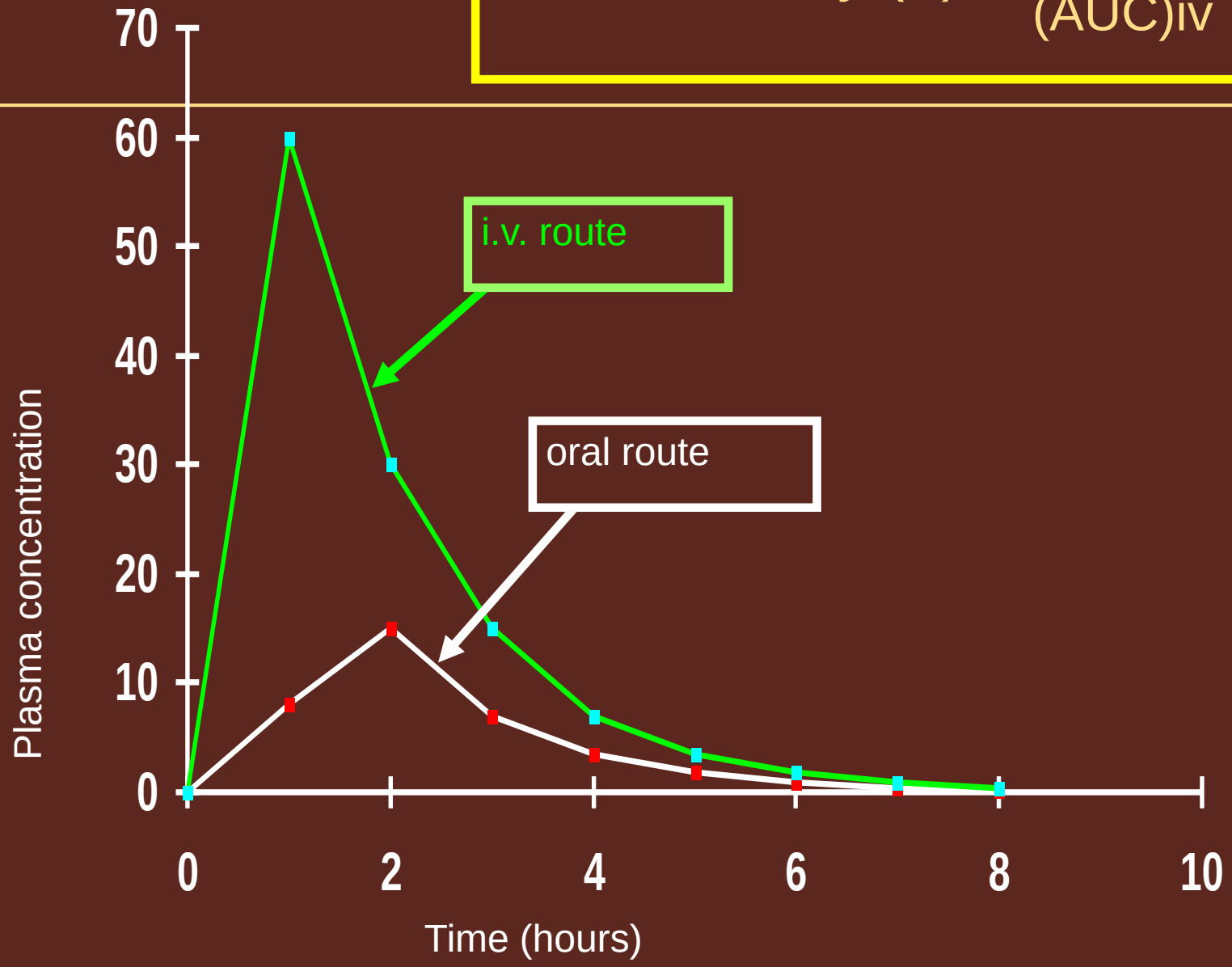
- The determination of relative bioavailability is very important in generic drug studies (e.g., bioequivalence studies).

RELATIVE AND ABSOLUTE BIOAVAILABILITY

- Absolute bioavailability (F) is the fraction of drug systemically absorbed from the dosage form.

- F is calculated as the ratio of the AUC for the dosage form given orally to the AUC obtained after intravenous (IV) drug administration (adjusted for dose).

$$\text{Bioavailability (F)} = \frac{\text{(AUC)po}}{\text{(AUC)iv}}$$



RELATIVE AND ABSOLUTE BIOAVAILABILITY

- A parenteral drug solution given by IV administration is considered to have 100% systemic absorption (i.e., F = 1).

- An F value of 0.80 (or 80%) indicates that only 80% of the drug was systemically available from the oral dosage form.

Route	Bioavailability (%)	Characteristics
Intravenous	100 (by definition)	Most rapid onset
Intramuscular	75 to ≤ 100	Large volumes feasible; painful
Subcutaneous	75 to ≤ 100	Smaller volumes than IM; may be painful
Oral	5 to ≤ 100	Most convenient; first pass effect may be significant
Rectal	30 to ≤ 100	Less first pass effect than oral
Inhalation	5 to ≤ 100	Often very rapid onset
Transdermal	80 to ≤ 100	Usually very slow absorption; lack of first pass effect; prolonged duration of action

RELATIVE AND ABSOLUTE BIOAVAILABILITY

RELATIVE Bioavailability

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

Comparison here is between

2 ORAL Formulations

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 AND ABSOLUTE BIOAVAILABILITY

Relative Availability

Relative availability is determined for various drugs

- using plasma data

$$\text{relative availability} = \frac{[AUC]_{\text{new drug}} / D_{\text{new drug}}}{[AUC]_{\text{ref. drug}} / D_{\text{ref. drug}}}$$

- using urine data

$$\text{relative availability} = \frac{(D_u)_{\text{new drug}} / D_{\text{new drug}}}{(D_u)_{\text{ref. drug}} / D_{\text{ref. drug}}}$$

Absolute Availability

Absolute availability is determined for the same drug in various formulations

- using plasma data

$$\text{absolute availability} = \frac{[AUC]_{\text{new form.}} / D_{\text{new form.}}}{[AUC]_{\text{ref. form.}} / D_{\text{ref. form.}}}$$

- using urine data

$$\text{absolute availability} = \frac{(D_u)_{\text{new form.}} / D_{\text{new form.}}}{(D_u)_{\text{ref. form.}} / D_{\text{ref. form.}}}$$

- subscripts: new formulation - tested formulation,
  reference - usually IV injection

Bioavailability calculation

- Bugstatin Bugstatin at a dose of 60 mg achieves at AUC_{IV}= 10 mg.hr/L and AUC_{po}= 7.5 mg.hr/L.
- What is the oral bioavailability ?
  - 0.75
- What oral dose is required to achieve the same drug exposure as an IV dose of 60 mg?
  - 80 mg

Design of Bioequivalence Studies

- For many drug products, the Division of Bioequivalence, Office of Generic Drugs (FDA) provides guidance for the performance of *in vitro* dissolution and *in vivo* bioequivalence studies.

Design of Bioequivalence Studies

- **Fasting study**.

- Bioequivalence studies are usually evaluated by a single-dose, two-period, two-treatment, two-sequence, open-label, randomized crossover design, comparing equal doses of the Test (generic) and Reference (brand) products in fasted, adult, healthy subjects.

Design of Bioequivalence Studies

- **Fasting study**.

- Both men and women may be used in the study.
- Blood sampling is performed just before the dose (zero time) and at appropriate intervals after the dose to obtain an adequate description of the plasma drug concentration versus time profile.

Design of Bioequivalence Studies

- **Food intervention study.**
- If the bioavailability of the *active* drug ingredient is known to be affected by food, the generic drug manufacturer must include a single-dose, randomized, *crossover, f*ood effects study comparing equal doses of the Test product and Reference products *given* immediately after a standard high-fat content breakfast.

Design of Bioequivalence Studies

- **Waiver of an *in vivo* bioequivalence study**
- A comparative *in vitro* dissolution (drug release) study between the Test and Reference products may be used in lieu of an *in vivo* bioequivalence study for some immediaterelease (conventional) oral drug products.

Pharmacokinetic evaluation of the data

- **Single-dose studies.**

- Pharmacokinetic analysis includes calculation for each subject of the AUC to the last quantifiable concentration (AUC_{o-t}) and to infinity ($AUC_{o-\infty}$), T_{max} and C_{max}. Additionally, the elimination rate constant (k), the elimination half-life ($t_{1/2}$) and other parameters may be estimated.

Statistical evaluation of the data

- Bioequivalence of two different formulations of the same drug substance *involves* equivalence with respect to the rate and extent of drug absorption.
- If the bioavailability of the two formulations differs by -20%/+25% or less, then the products are generally considered bioequivalent.
- The use of the - 20%/+ 25% or less rule is based on a medical decision that this difference in plasma drug concentration will not be clinically significant.

Statistical evaluation of the data

- analysis of variance (**ANOVA**)
- 90% confidence intervals

- There should be no statistical differences between the mean AUC and C_{max} parameters for the Test (generic) and Reference drug products. should not be less than 0.80 (80%) nor greater than 1.25 (125%)

- *i.e. bioequivalence interval* (80%-125%)

Table. Bioavailability Comparison of a Generic (Test) and Brand (Reference) Drug Product

Parameter	Units	Test	Reference	(%) T/R	90% Confidence Limits
AUC_{o-t}	µg hr/ml	1466	1494	98.1	93.0-102.5
$AUC_{o-\infty}$	µg hr/ml	1592	1606	99.1	94.5-104.1
C_{max}	µg hr/ml	11.6	12.5	92.8	88.5-98.6
T_{max}	hr	1.87	2.10	89.1	

The results were obtained from a two-way crossover, single dose, fasting study in 24 healthy adult volunteers. Mean values are reported. No statistical differences were observed between AUC and C_{max} values for the Test and Reference products.

BIOEQUIVALENCE ISSUES

- Problems in determining bioequivalence include lack of an adequate study design, inability to accurately measure the drug analytes including metabolites and enantiomers (chiral drugs), and lack of systemic drug absorption (Table.)

Problem Issues	Example
Drugs with highly variable bioavailability	Propranolol, verapamil
Drugs with active metabolites	Selegilene
Chiral drugs	Ibuprofen, albuterol
Drugs with nonlinear pharmacokinetics	Phenytoin
Orally administered drugs that are not systemically absorbed	Cholestyramine resin, sulcralfate
Drugs with long elimination half-lives	Probucol
Nonoral drug delivery Topical drugs Transdermal delivery systems Inhalation aerosols Intranasal drugs	 Steroids, antifungals Estrogen patch Bronchodilators, steroids Intranasal steroids
Biotechnology derived drugs	Erythropoietin, interferon
Bioavailable drugs that should not reach peak drug levels	Potassium supplements, hormone replacement therapy
Target population used in the bioequivalence studies	Pediatric patients; renal disease

BIOEQUIVALENCE ISSUES

- Bioequivalence studies for which objective blood drug concentrations cannot be obtained require either a pharmacodynamic study, clinical trial, or an *in vitro* study that has been correlated with human *in vivo* bioavailability data.

TABLE 16-2 Examples of Drug Products for Which FDA Recommends That Bioequivalence Studies Use Pharmacodynamic Endpoints

Drug Product	Indication	Mechanism of Action	Endpoint
Acarbose tablet (if no Q1/Q2 sameness between test and reference)	Treatment of type 2 diabetes	Inhibition of intestinal α-glucosidase, thereby decreasing absorption of starch and oligosaccharides	Reduction in blood glucose concentrations
Lanthanum carbonate tablet	Reduction of serum phosphate levels in patients with end-stage renal disease	Inhibits phosphate absorption by forming highly insoluble lanthanum phosphate complexes in GI tract	Reduction in urinary phosphate excretion
Orlistat capsules	Treatment of obesity	Inhibition of intestinal lipase, thereby reducing absorption of free fatty acids and monoacylglycerols	Amount of fat excreted in feces over 24 hours at steady state
Fluticasone propionate cream	Relief of skin itching and inflammation	The application of corticosteroids causes blanching in the microvasculature of the skin (not the mechanism of action, but quantitatively measurable)	Skin chromameter measurements through at least 24 hours after application

The data in Table 16-22 represent the average findings in antibiotic plasma samples taken from 10 humans (average weight 70 kg), tabulated in a 4-way crossover design.

- A.Which of the four drug products in Table 16-22 would be preferred as a reference standard for the determination of relative bioavailability? Why?
- **b. From which oral drug product is the drug absorbed more rapidly?**
- **c. What is the absolute bioavailability of the drug from the oral solution?**
- **d. What is the relative bioavailability of the drug from the oral tablet compared to the reference standard?**
- **e. From the data in Table 16-15, determine:**
  - **(i) Apparent *VD***
  - **(ii) Elimination *t1/2***
  - **(iii) First-order elimination rate constant *k***
  - **(iv) Total body clearance**

TABLE 16-22 Comparison of Plasma Concentrations of Antibiotic, as Related to Dosage Form and Time

	Plasma Concentration (μg/mL)			
Time after Dose (h)	IV Solution (2 mg/kg)	Oral Solution (10 mg/kg)	Oral Tablet (10 mg/kg)	Oral Capsule (10 mg/kg)
0.5	5.94	23.4	13.2	18.7
1.0	5.30	26.6	18.0	21.3
1.5	4.72	25.2	19.0	20.1
2.0	4.21	22.8	18.3	18.2
3.0	3.34	18.2	15.4	14.6
4.0	2.66	14.5	12.5	11.6
6.0	1.68	9.14	7.92	7.31
8.0	1.06	5.77	5.00	4.61
10.0	0.67	3.64	3.16	2.91
12.0	0.42	2.30	1.99	1.83
AUC $\left(\frac{\mu g}{mL} \times h\right)$	29.0	145.0	116.0	116.0