

Principles of Drug Delivery

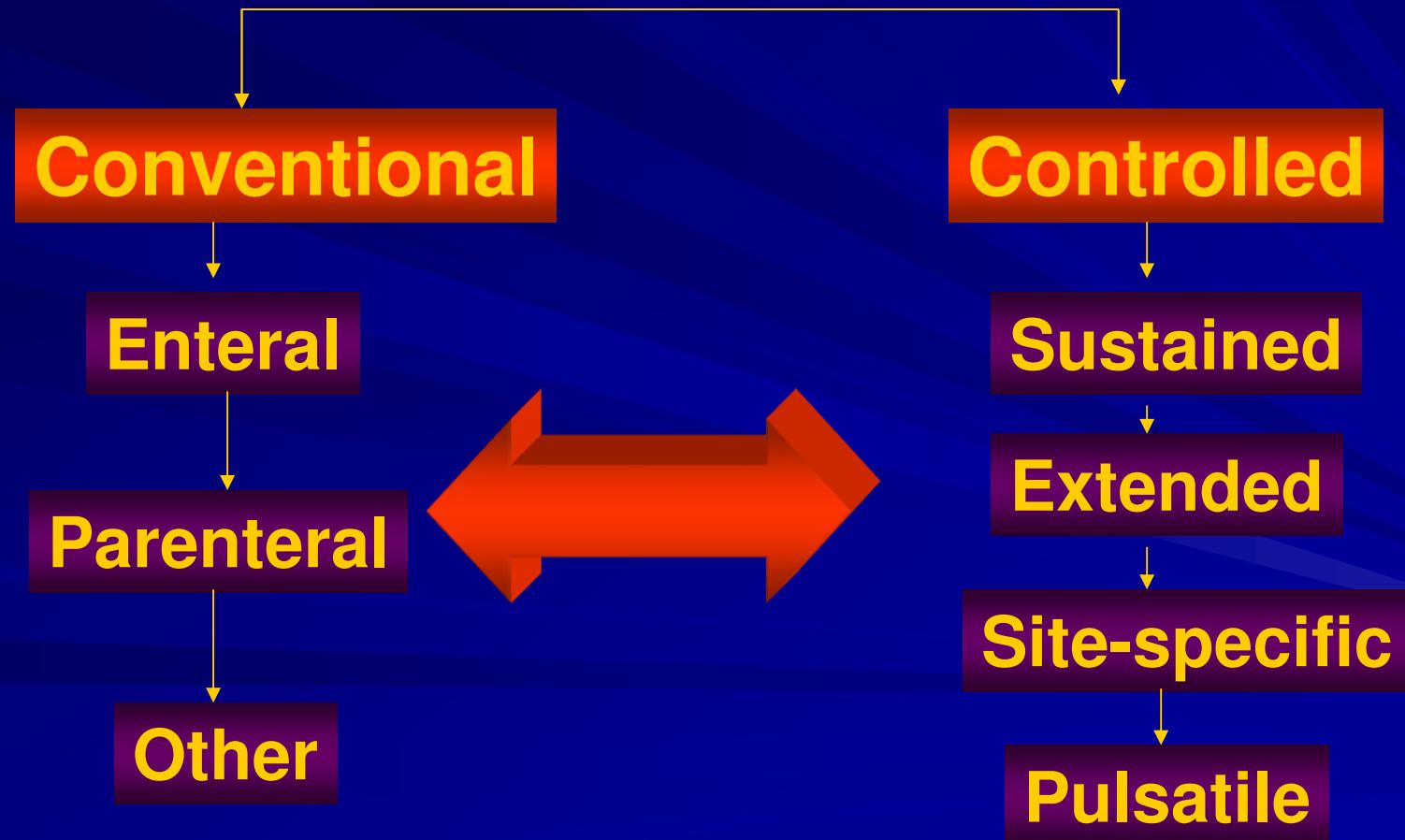
Drug Delivery

■ Definition

- The appropriate administration of drugs through various routes in the body for the purpose of improving health
- It is highly interdisciplinary
- It is not a young field
- It has recently evolved to take into consideration
 - Drug physico-chemical properties
 - Body effects and interactions
 - Improvement of drug effect
 - Patient comfort and well being

Controlled
Drug Delivery

Drug Delivery



Oral Administration

■ Advantages

- Patient: Convenience, not invasive, higher compliance
- Manufacture: well established processes, available infrastructure

■ Disadvantages

- Unconscious patients cannot take dose
- Low solubility
- Low permeability
- Degradation by GI enzymes or flora
- First pass metabolism
- Food interactions
- Irregular absorption

Oral Administration

- Traditional oral delivery systems
 - Tablets
 - Capsules
 - Soft gelatin capsules
 - Suspensions
 - Elixirs



Buccal/Sublingual

■ Advantages

- By-pass First pass metabolism
- Rapid absorption
- Low enzymatic activity

■ Disadvantages

- Discomfort during dissolution
- Probability of swallowing- lost of effect
- Small doses

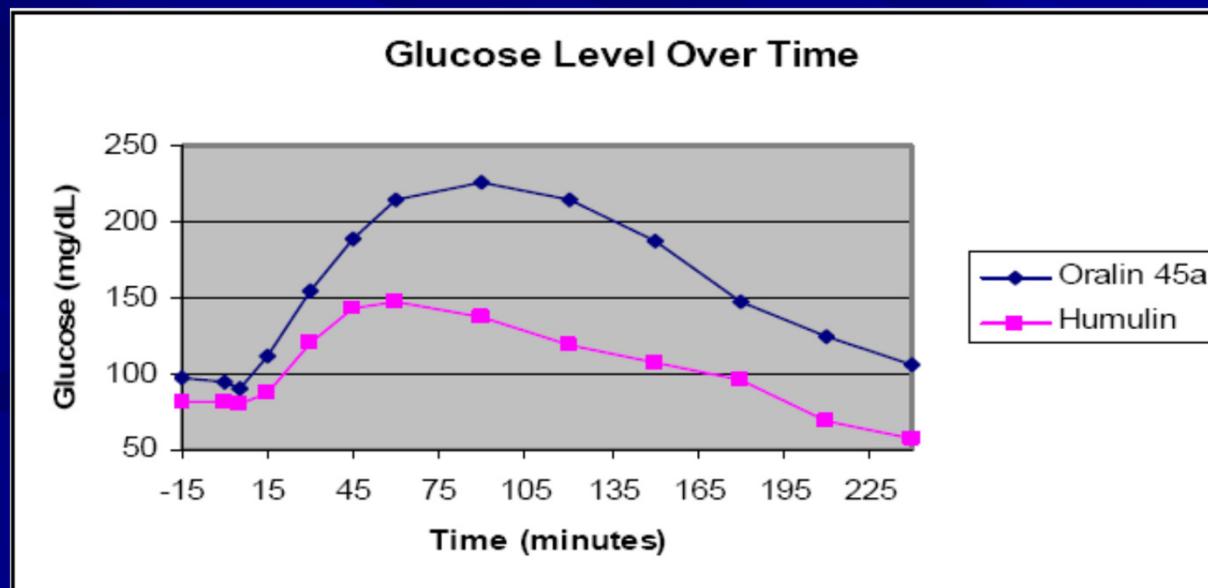
■ Traditional delivery system/devices

- Tablets
- Chewing gum



Example from Industry: Generex Biotechnology

- Oral-Lyn: liquid formulation of human insulin administered to buccal mucosa by aerosolization
 - Drug carried in lipid micelles



Rectal

■ Advantages

- By-pass first pass metabolism
- Useful for children

■ Disadvantages

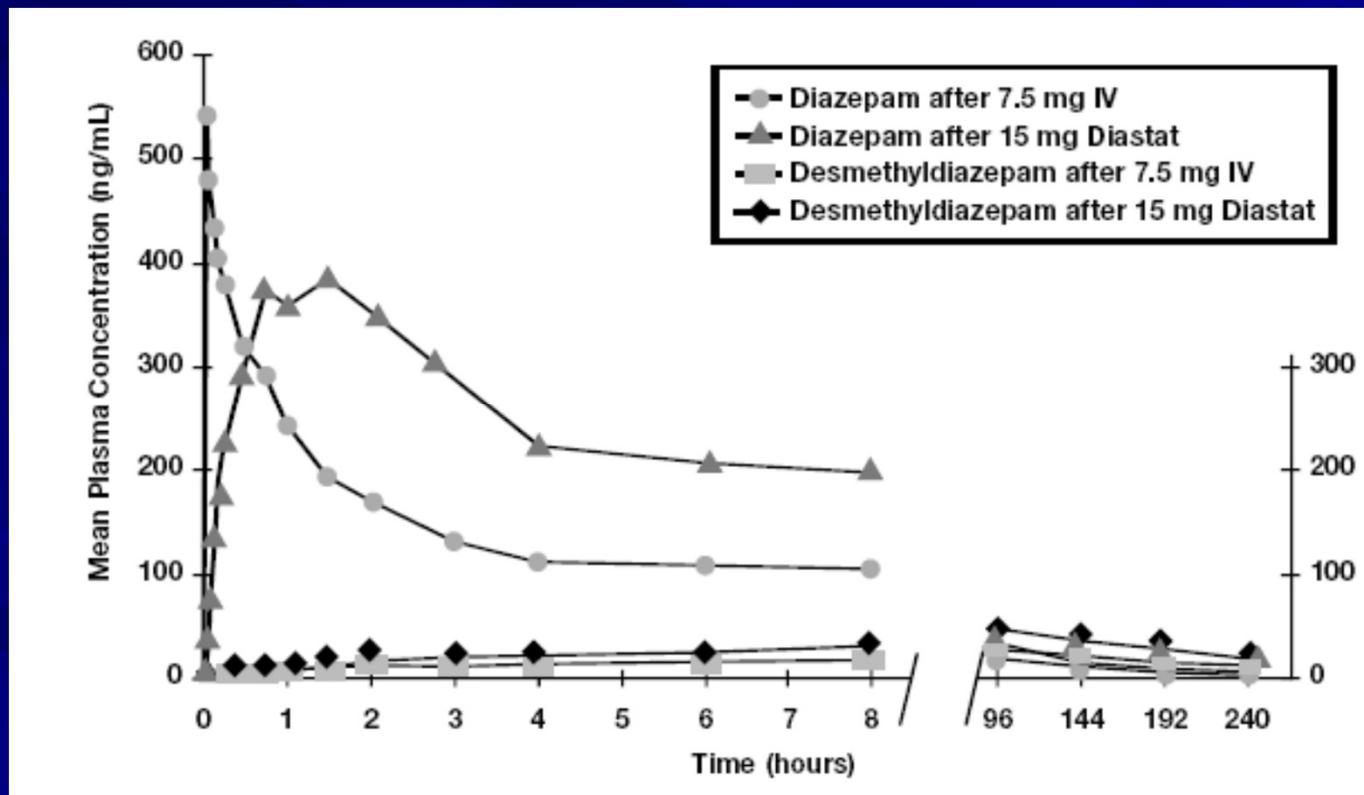
- Absorption depends on disease state
- Degradation by bacterial flora
- Uncomfortable

■ Traditional delivery system/devices

- Suppository
- Enema

Example from Industry: Valeant Pharmaceuticals

- Diastat AcuDial: diazepam rectal gel



Intravenous (IV)

■ Advantages

- Drug 100% bioavailable
- Rapid response
- Total control of blood concentration
- Maximize incorporation of degradable drugs
- By-pass FPM

■ Disadvantages

- Invasive
- Trained personnel
- Possible toxicity due to incorrect dosing
- sterility

■ Traditional delivery system/devices

- Injection-bolus
- IV bag - infusion



Subcutaneous

■ Advantages

- Patient self-administration
- Slow, complete absorption
- By-pass FPM

■ Disadvantages

- Invasive
- Irritation, inflammation
- Maximum dose volume - 2mL

Intramuscular

■ Advantages

- Patient can administer the drug himself
- Larger volume than subcutaneous
- By-pass first pass metabolism

■ Disadvantages

- Invasive – patient discomfort
- Irritation, inflammation
- May require some training

Inhalers

■ Advantages

- By-pass FPM
- Gases are rapidly absorbed

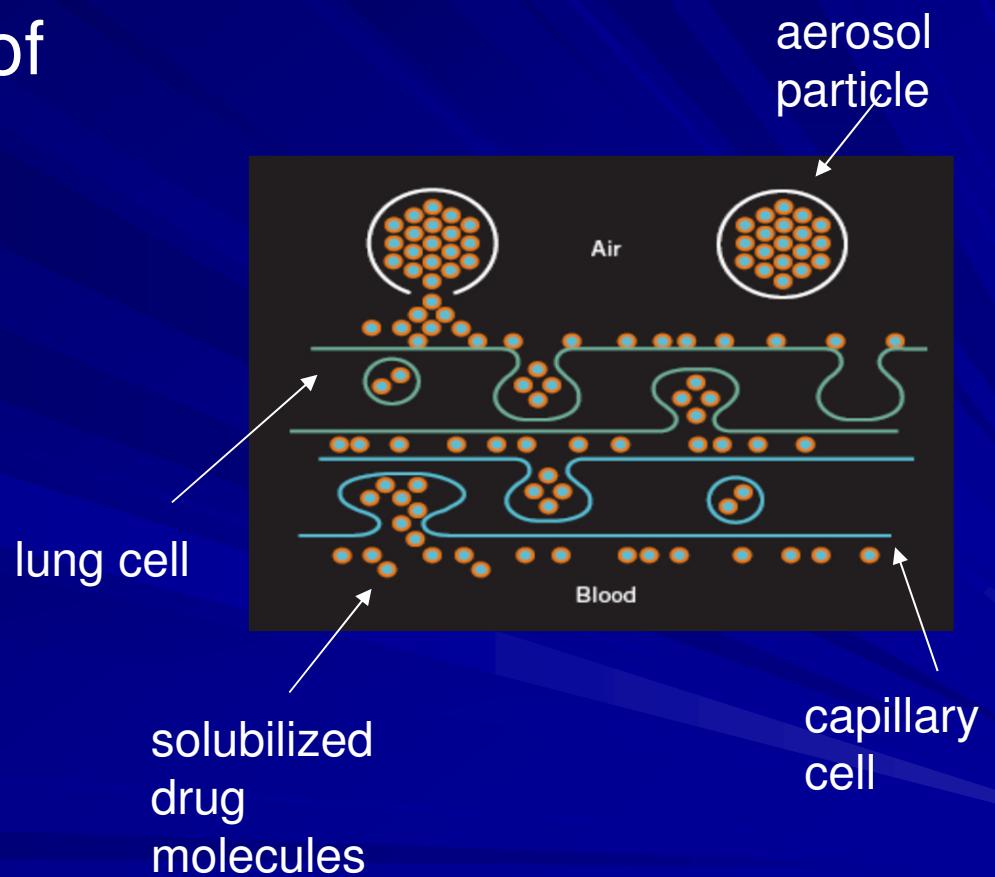
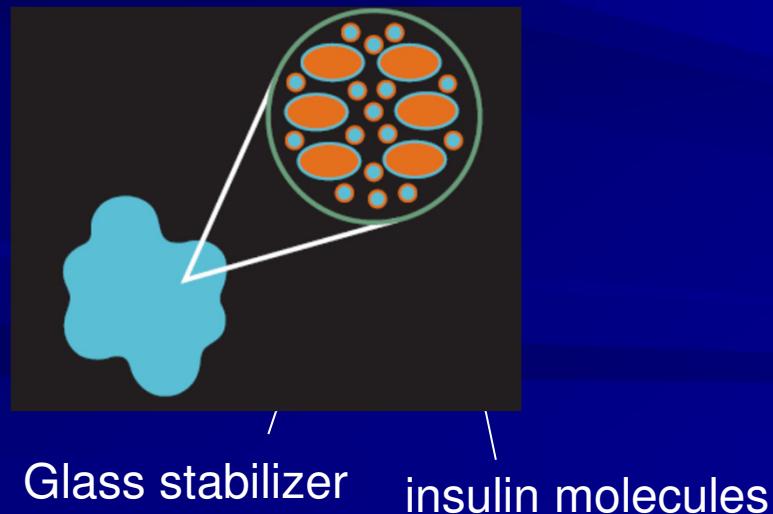
■ Disadvantages

- Solids and liquids can be absorbed if size is below 0.5um

Example from Industry: Nektar Therapeutics

- Pulmonary delivery of Insulin

- Amorphous aerosol particles with $\sim 1\mu\text{m}$ diameters



Transdermal

■ Advantages

- Local effect
- Ease of administration

■ Disadvantages

- Low absorption for some drugs
- May cause allergic reactions

■ Requirements

- Low dosage <10 mg/mL
- MW< 1,000

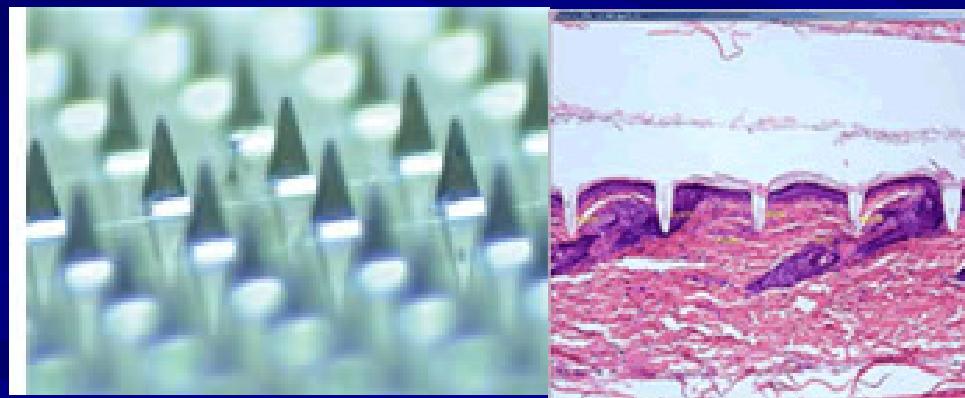


Factors Influencing the Selection of the Delivery Route

- Drug physico-chemical properties
 - Drug molecular size (molecular weight)
 - Half-life
 - Chemical stability
 - Loss of biological activity in aqueous solution
- Proteins
 - Denaturation, degradation

Example from Industry: 3M Company

- Microstructured Transdermal System: MTS
 - Microneedle system
 - Drug-in-adhesive technology platform



(a) 3M microneedle system and (b)
histological section of microneedles in
guinea pig skin

Factors Influencing the Selection of the Delivery Route

- Solubility in aqueous solution (hydrophobicity/hydrophilicity)
 - pH
 - pKa - ionization
 - Temperature
 - Concentration
 - Crystallinity
 - Particle size
 - State of hydration

Factors Influencing the Selection of the Delivery Route

■ Drug biological interactions

- Sensitive to FPM
- Low membrane permeability
 - Efflux pumps (MRP, MDR) – cancer drugs
 - Hydrophilicity
 - High-density charge
- Enzymatic degradation
- Bacterial degradation
- Half-life
- Side effects
 - Irritation

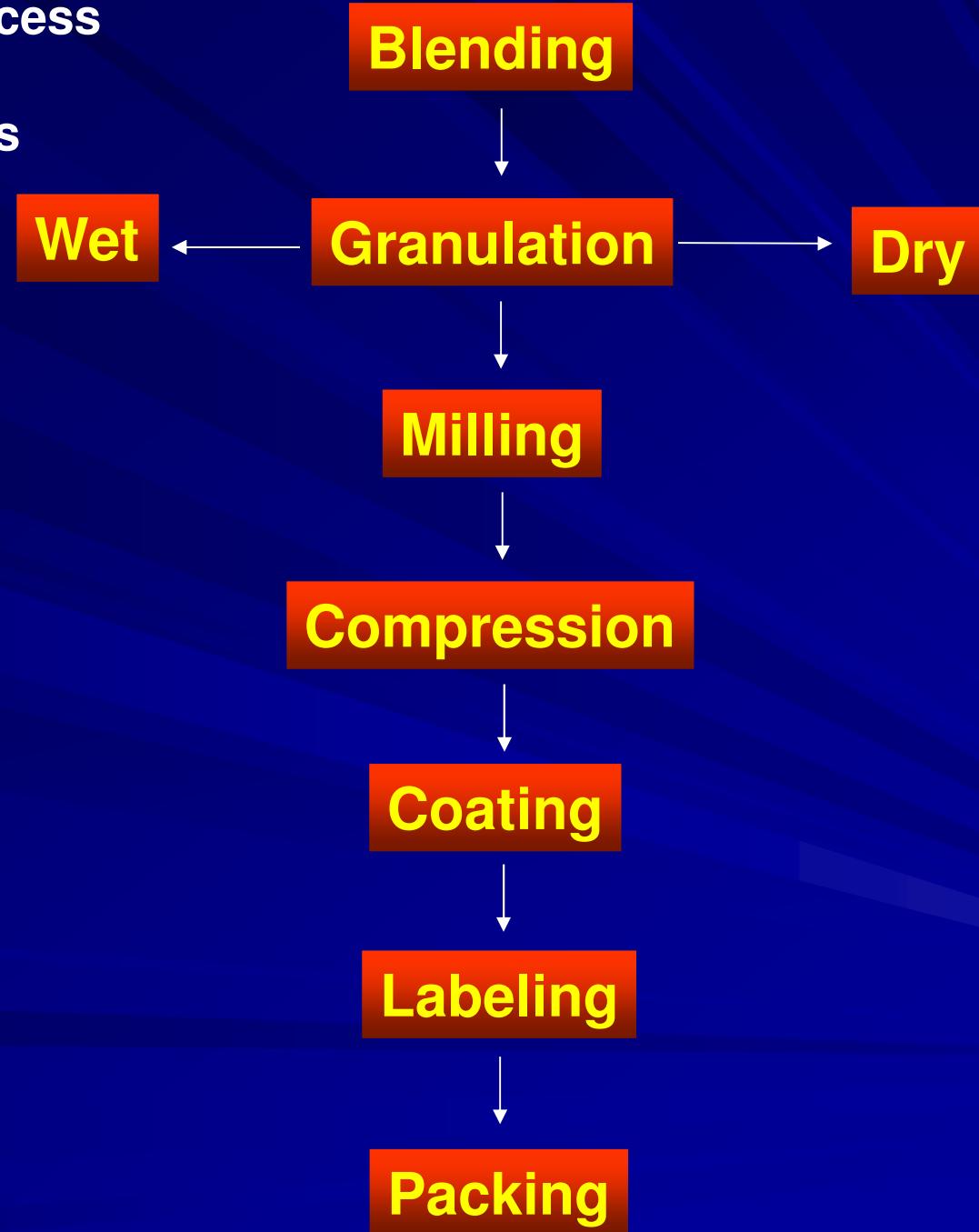
Factors Influencing the Selection of the Delivery Route

- Desired pharmacological effect
 - Local
 - topical, vaginal
 - Systemic
 - oral, buccal, IV, SC, IM, rectal, nasal
 - Immediate response
 - IV, SC, IM, nasal
 - Dose size
 - Drug molecular size

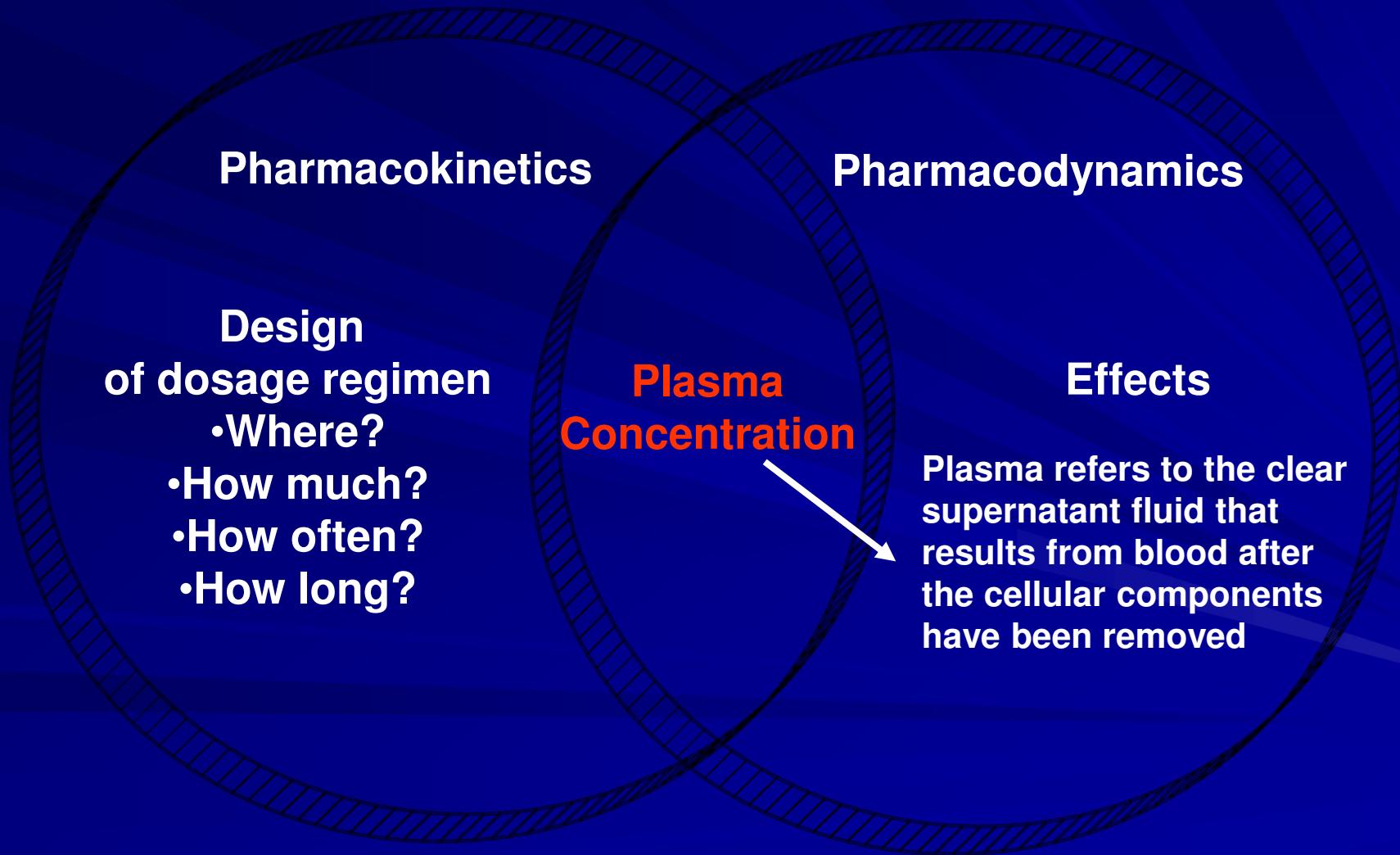
Manufacture of Classical Oral Delivery Systems

- **Formulation** – combination of active ingredients with the appropriate excipients
- **Excipients** – inactive ingredients employed for the purpose of dilution, protection, stability, controlled release, taste, fillers, coloring, disintegration, etc

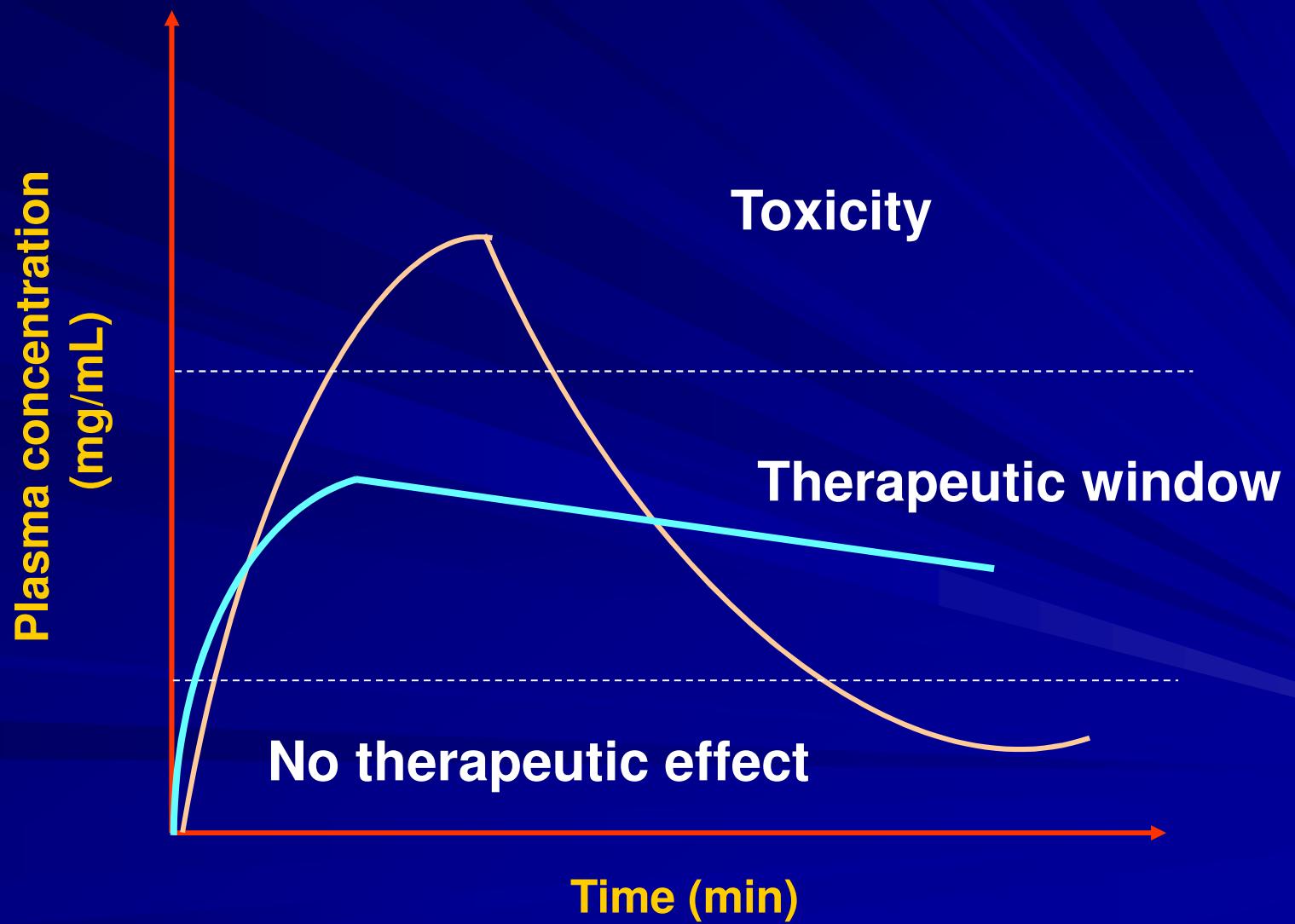
Manufacture Process for Tablets and Capsules

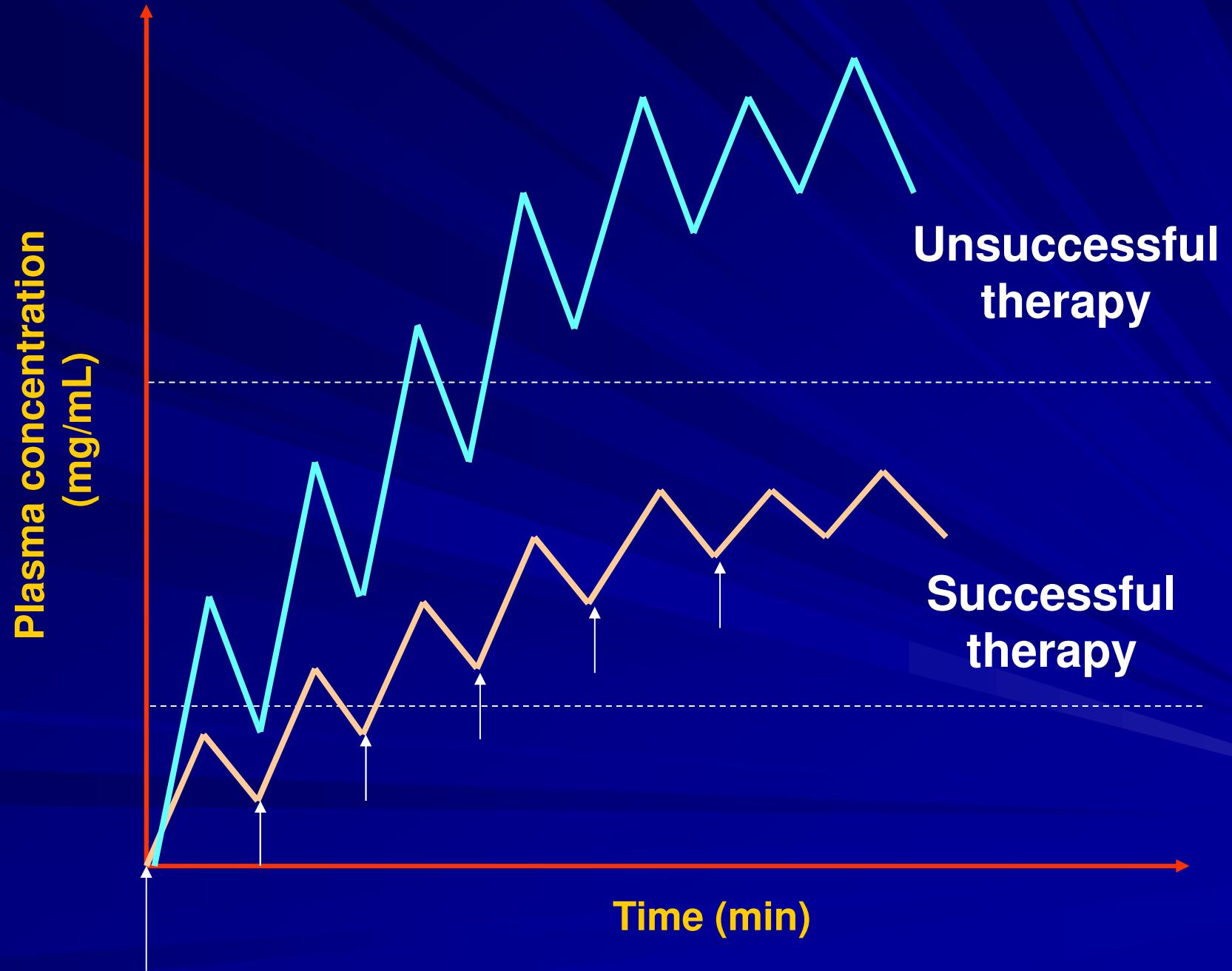


Pharmacokinetics and Pharmacodynamics



Plasma Concentration





Magnitude of Drug Response

- Depends upon concentration achieved at the site of action
 - Dosage
 - Extent of absorption
 - Distribution to the site
 - Rate/extent of elimination

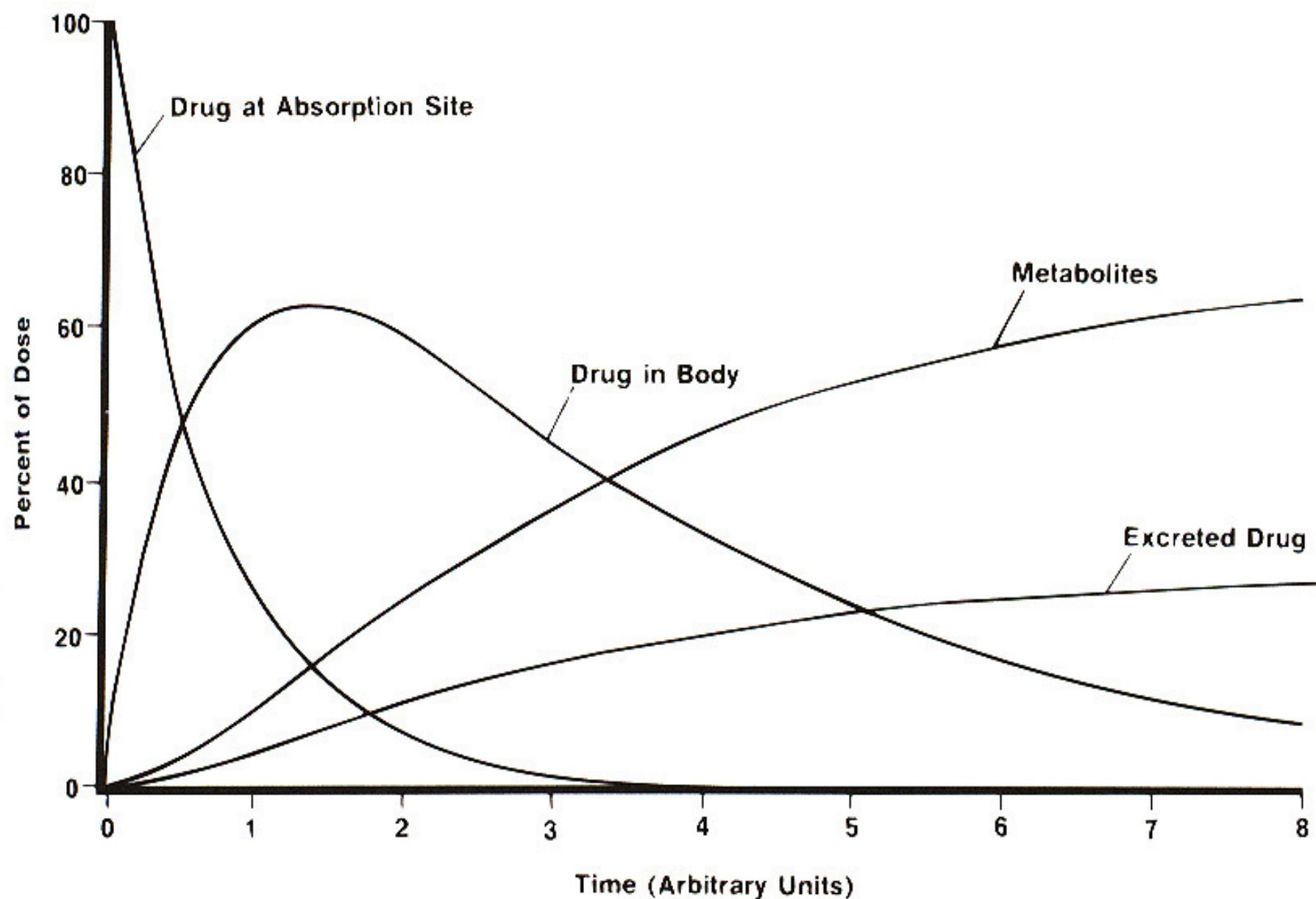


Fig. 3-5. Time course of drug in the body. (From Rowland, M., and Tozer, T.N.: Clinical Pharmacokinetics. 2nd Ed., Philadelphia, Lea & Febiger, 1989.)

From the Site of Delivery to Elimination...

steps in drug delivery, absorption, distribution and elimination

- Drug Delivery
 - Selection of drug delivery route
 - Knowledge of physicochemical properties
 - Design of dosing regimen
- Absorption
 - Knowledge of PK and PD
 - First pass effect
 - MDR or MRP

From the Site of Delivery to Elimination...

steps in drug delivery, absorption, distribution and elimination

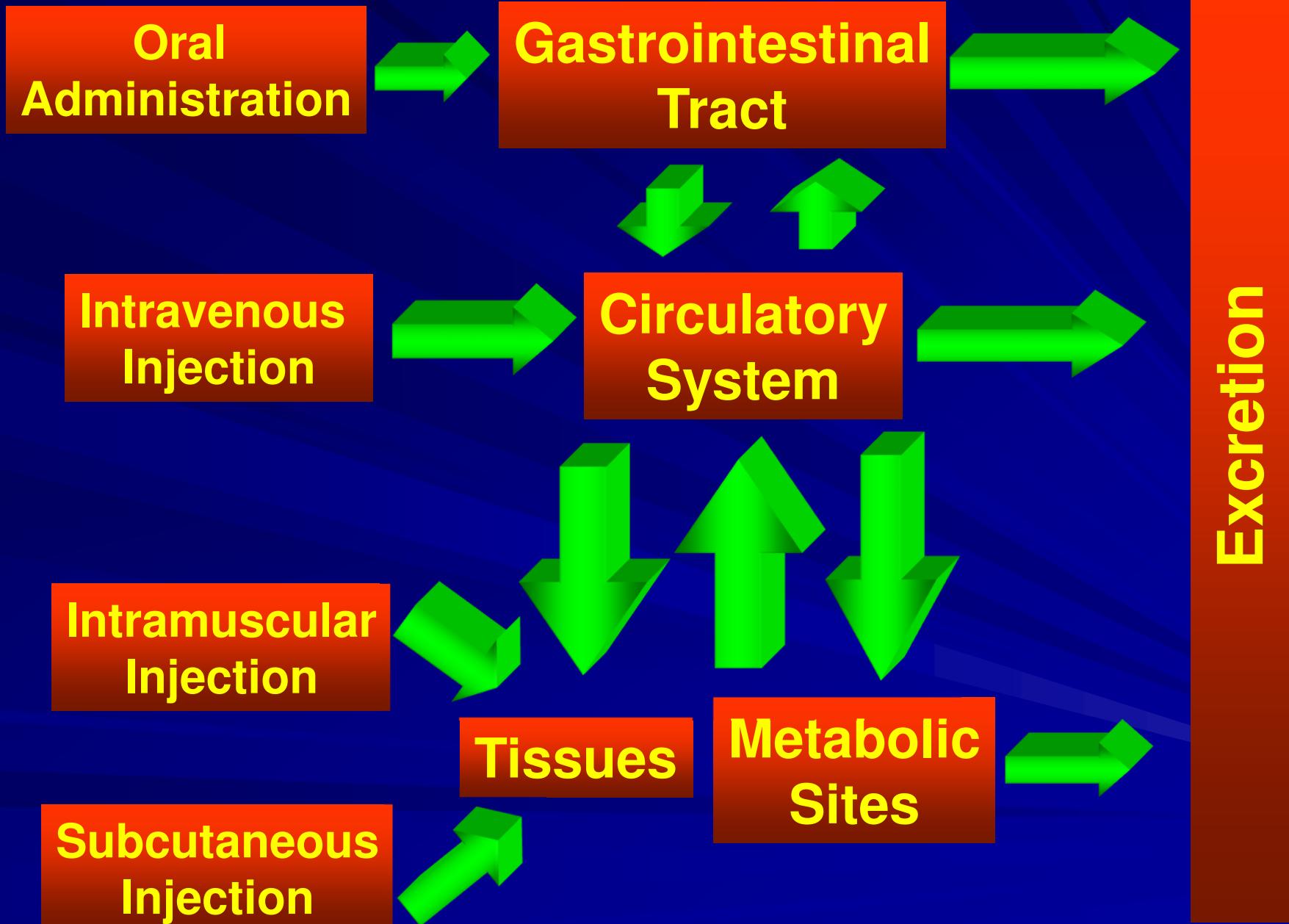
■ Distribution

- Drugs must reach the site of action

- Tissue
 - Plasma
- } Depends upon drug binding capabilities

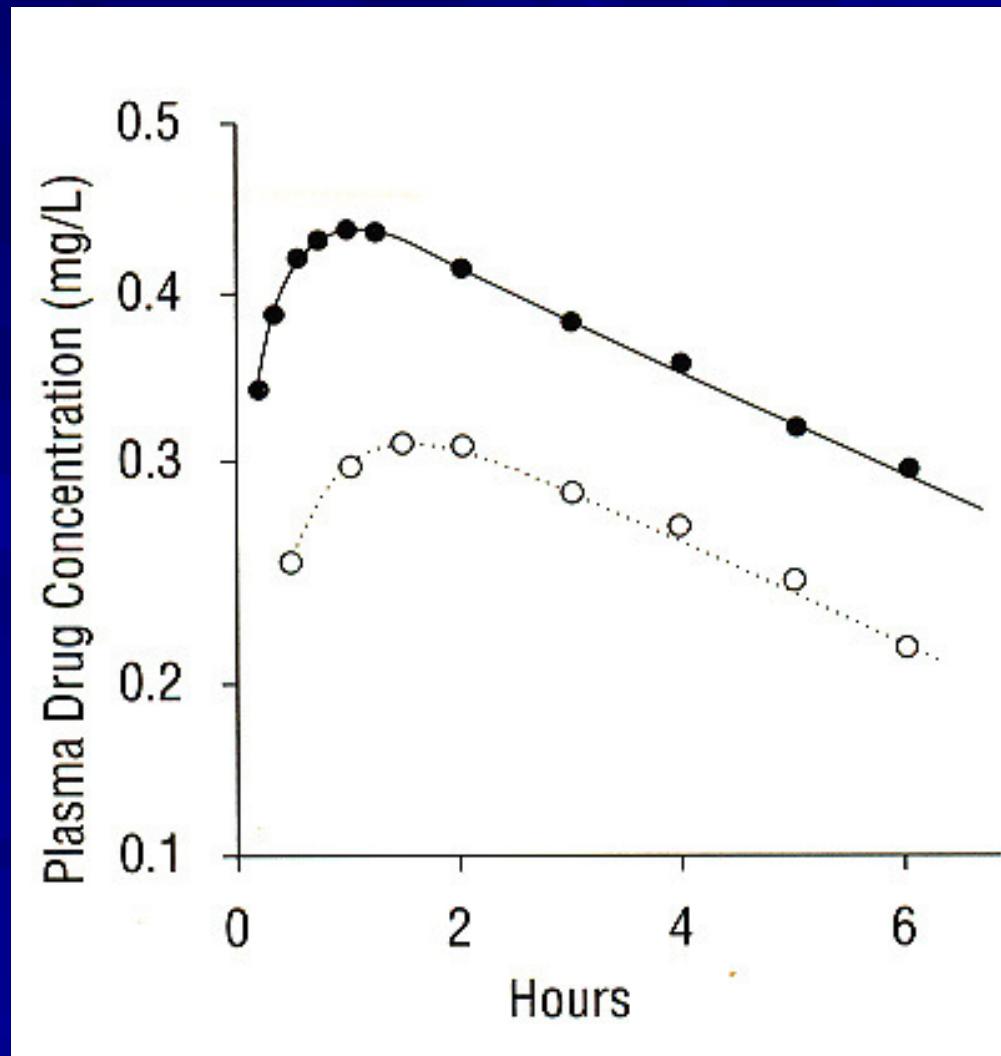
■ Elimination

- Metabolism
 - Liver, kidneys, cells
- Excretion
 - Kidneys
 - Feces

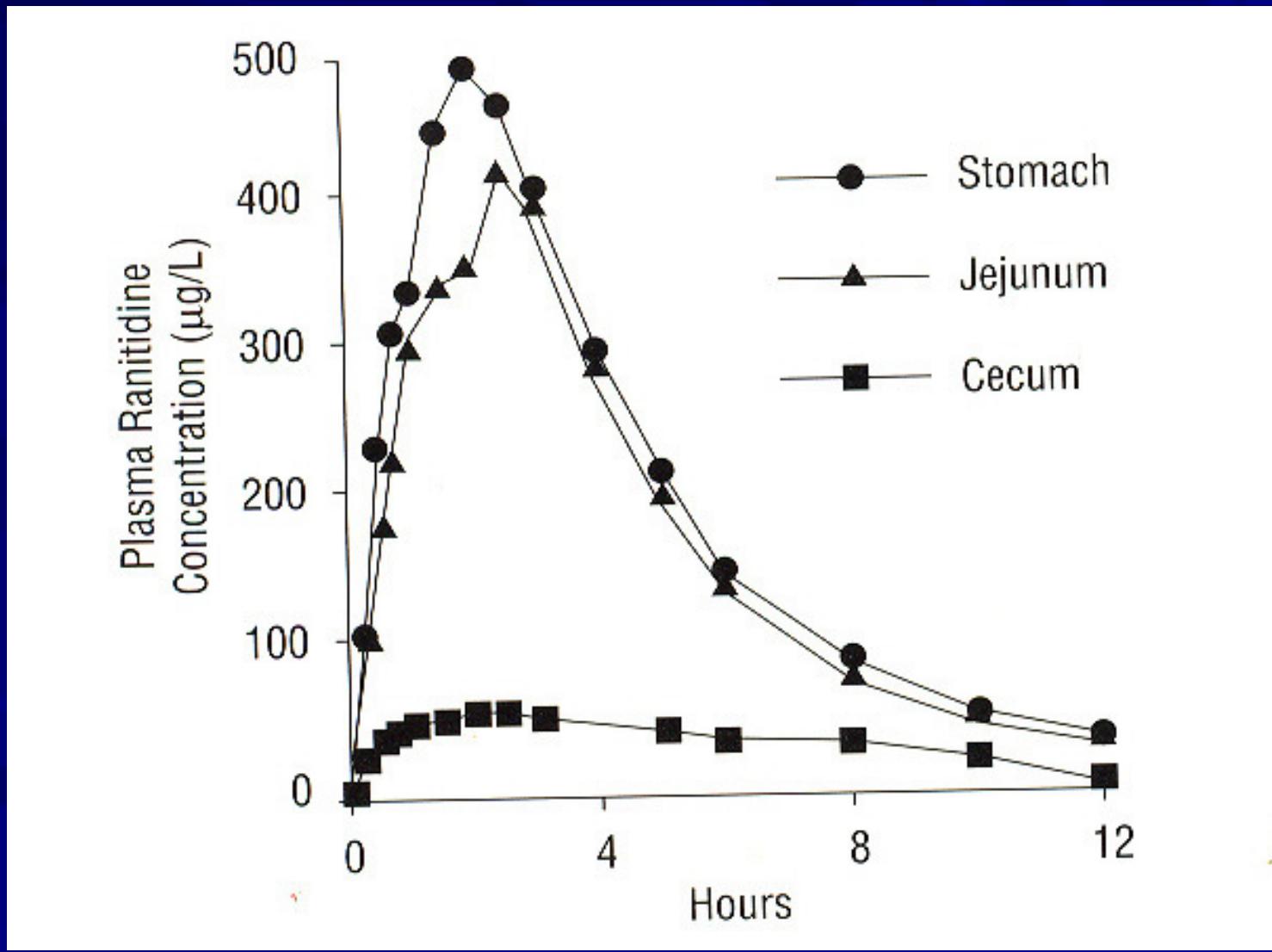


Absorption of drugs could vary within different administration routes

- 500 mg dose given
 - ● intramuscularly
 - ○ orally
- **to the same subject on separate occasions
- Biological barriers greatly affect the extent of drug absorption



- Absorption of drugs could vary within the same administration route



Important Concepts

■ Volume of distribution

- apparent volume into which a drug distributes in the body at equilibrium
- direct measure of the extent of distribution
- $V = \frac{A}{C}$ amount of drug in the body/Plasma drug concentration

$$V = \frac{A}{C}$$

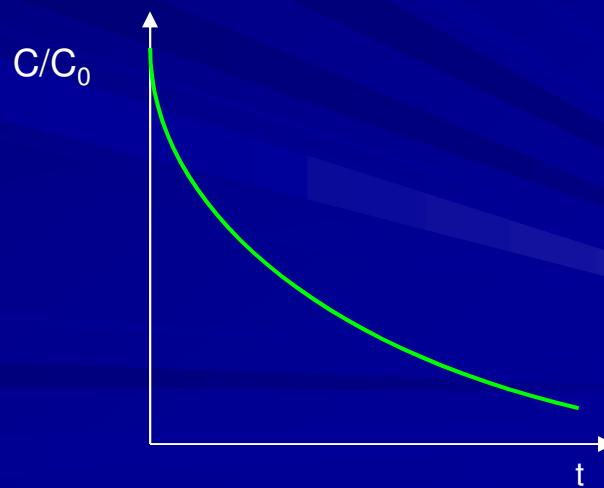
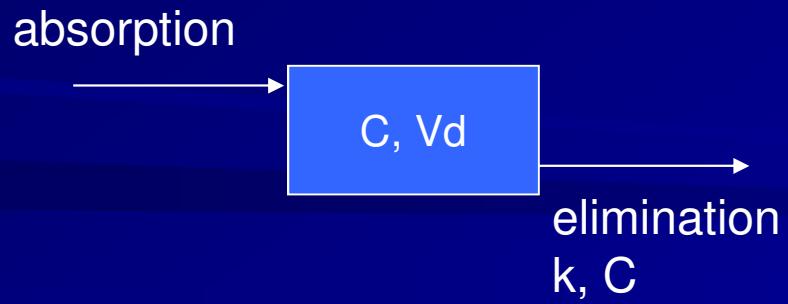
Mathematical Modeling of Drug Disposition

- Single compartment
- Single compartment with absorption
- Two compartments
- Two compartments with absorption
- Physiological Models

Single Compartment Model

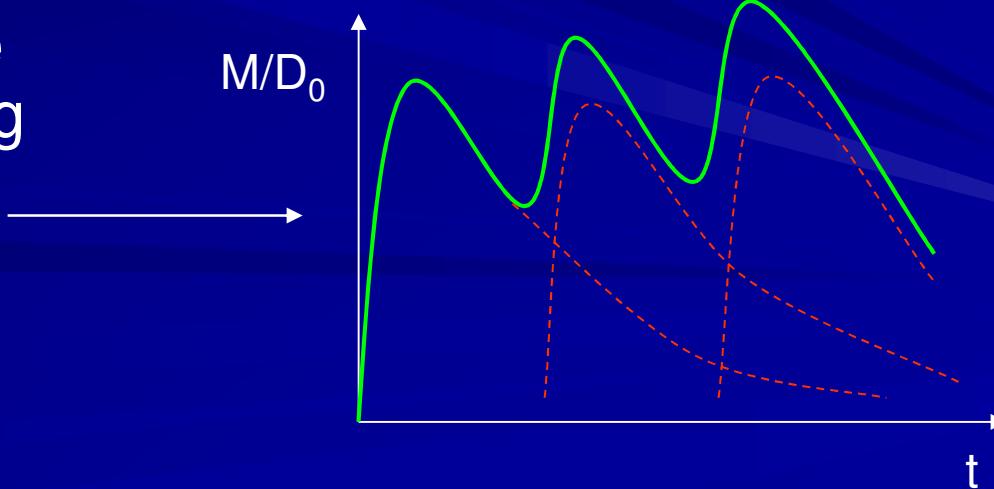
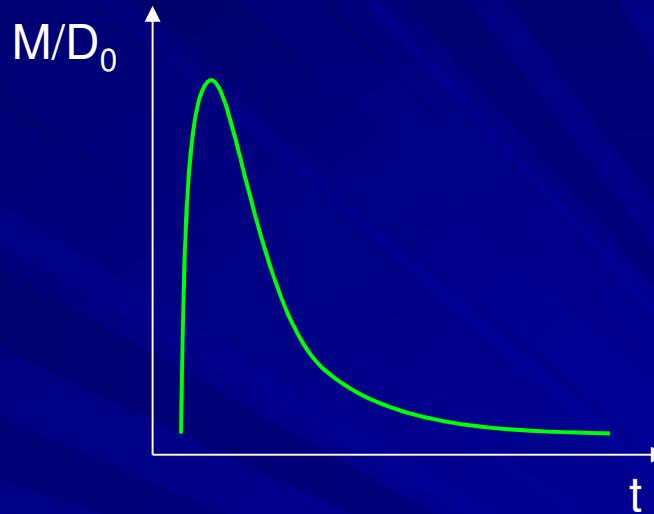
■ Assumptions:

- Body one compartment characterized by a volume of distribution (V_d)
- Drug is confined to the plasma (small V)



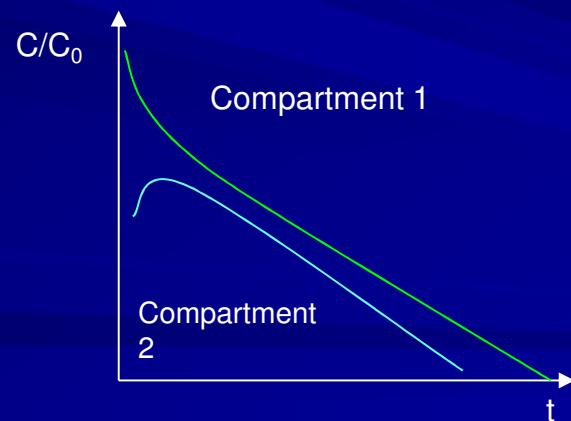
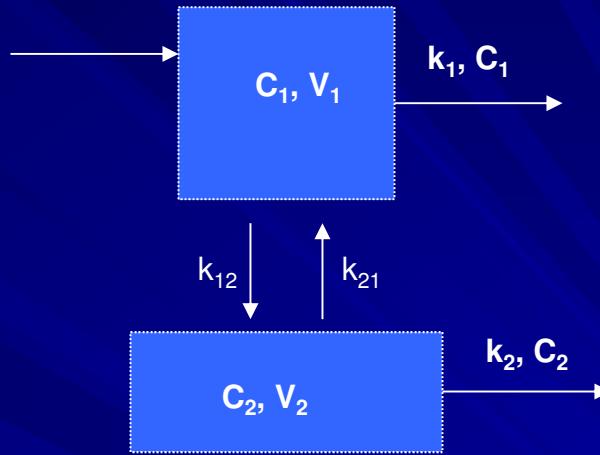
One-Compartment Model with Absorption

- Low absorption occurs
- Absorption is the rate-limiting step
- Slow absorption may represent drug entry through GI tract or leakage into circulation after SC injection
- Drugs require multiple doses to maintain drug concentration within therapeutic window

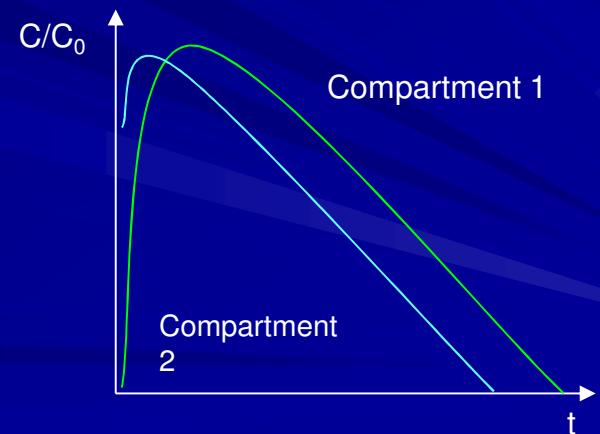


Two-Compartment Model

- Drug rapidly injected
- Drug distributed instantaneously throughout one compartment and slowly throughout second compartment
- Describes drug concentration in plasma injected IV



Concentration after ingestion



Concentration with slow absorption

Physiological Models

Determination of the Efficacy of the Delivery Route

■ Bioavailability (F)

- Fraction of the drug that reached the systemic circulation
- According to the FDA, Food, Drug, and Cosmetic Act
 - “The rate and extent to which an active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drugs that are not intended to be absorbed in the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.”

Factors Influencing Bioavailability

- Delivery route
- The site of measurement
- Type of animal employed
- Physiological state of the animal/human
 - Disease
 - Anesthesia

Implications of PK and PD in Drug Delivery

- The PK and PD of a drug may be affected when administered via different routes
 - Examples
 - Proteins – oral vs. intramuscular
 - Morphine – oral vs. intramuscular
- The PK and PD of a drug delineates its therapeutic window
 - Degree of absorption
 - Degree of elimination and/or metabolism
 - Example
 - Tetracycline (infection) – given 6 to 8 hours
 - Digoxin (cardiac failure) – given daily

Where to Find PD and PK Information

- United States Pharmacopeia
 - www.usp.org
 - It is also paper published
 - Provides standards, chemical properties, and protocols to perform pharmacological experiments
- Federal Drug Administration – if it has already being approved
 - www.fda.org