DRUG FORMULATION & DRUG DELIVERY SYSTEM

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Role of the drug formulation on its delivery to systemic circulation

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.
- With any drug it is possible to alter its bioavailability considerably by formulation modification.
- Bioavailability of a drug from different dosage forms would decrease in the order solution > suspension > capsule > tablet > coated tablet.
- There may be some exceptions but the order provides a a useful guide as is the case with pentobarbital: aqueous solution > aqueous suspension = capsule > tablet of free acid form.

Solutions

- Drugs are commonly given in solution in cough/cold remedies and in medication for the young and elderly.

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

- The rate limiting step is often the rate of gastric emptying.

Solutions

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- A poor water soluble drug such as phenytoin presented as a well formulated suspension, of finely divided powder, may have a better bioavailability.

- Some drugs which are poorly soluble in water may be dissolved in mixed water/alcohol or glycerol solvents.

- This is particularly useful for compounds with tight crystal structure, higher melting points that are not ionic. The crystal structure is broken by solution in the mixed solvent.

Suspensions

- A well formulated suspension is second only to a solution in terms of superior bioavailability.
- Absorption may well be dissolution-limited, however a suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.

Suspensions

- With very fine particle sizes the dispersibility of the powder becomes important.

- The addition of a surface active agent will improve dispersion of a suspension
  - may improve the absorption of very fine particle size suspensions for which caking may otherwise be a problem.

Capsules

- **In theory a capsule dosage form should be quite efficient.**
- **The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.**
- **The capsule contents should not be subjected to high compression forces which would tend to reduce the effective surface area**

Capsules…..

- Thus a capsule should perform better than a tablet. This is not always the case.
- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation.
- These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

Tablets

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.
- The biggest problem is overcoming the reduction in effective surface area produced during the compression process.

Ingredients

- Tablet ingredients include materials to break up the tablet formulation - ??
- Drug - may be poorly soluble, hydrophobic
- Lubricant - usually quite hydrophobic
- Granulating agent - tends to stick the ingredients together

Tablet Ingredients

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- Filler - may interact with the drug, etc., should be water soluble
- Wetting agent - helps the penetration of water into the tablet
- Disintegration agent - helps to break the tablet apart
- Coating agent – places additional barrier to drug dissolution.

Sustained release tablets

- “Modified release Dosage forms” This topic and the area of sustained release products will be discussed in more detail in other courses.

- **Benefits**

- for short half-life drugs, sustained release can mean less frequent dosing and thus better compliance.

- reduce variations in plasma/blood levels for more consistent result.

Problems with sustained-release drug formulations

- **More complicated formulation may be more erratic in result.**
- **A sustained release product may contain a larger dose, i.e. the dose for two or three (or more) 'normal' dosing intervals.**
- **A failure of the controlled release mechanism may result in release of a large toxic dose.**
- **More expensive technology**

In vitro dosage form testing & evaluation

- **Disintegration**
  - Disintegration time is the time to pass through a sieve while agitated in a specified fluid.
  - It indicates the time to break up into small particles, not necessarily the time to go into solution.

Dissolution Rate

- Assesses the time is takes for the drug to dissolve from the dosage form.
- Numerous factors affect dissolution.
  - Dissolution medium (may be water, simulated gastric juice, or 0.1M HCl))
  - Agitation intensity
  - Temperature (usually 37°C) are carefully controlled.
  - The apparatus and specifications may be found in the BP/USP.

Dissolution
Rate *Methodology*

- Other unofficial methods are used because they may be faster, cheaper, easier, sensitive to a particular problem for a particular drug, or developed by a particular investigator.

In-vitro/In vivo correlations (IVIVIC)

- Dissolution tests are used as quality control to measure variability between batches which may be reflected by *in vivo* performance.

- *In vitro* test may be a quick method of ensuring *in vivo* performance and considerable work aimed at defining the *in vitro*/*in vivo* correlation has been done.

Types of drugs and their forms

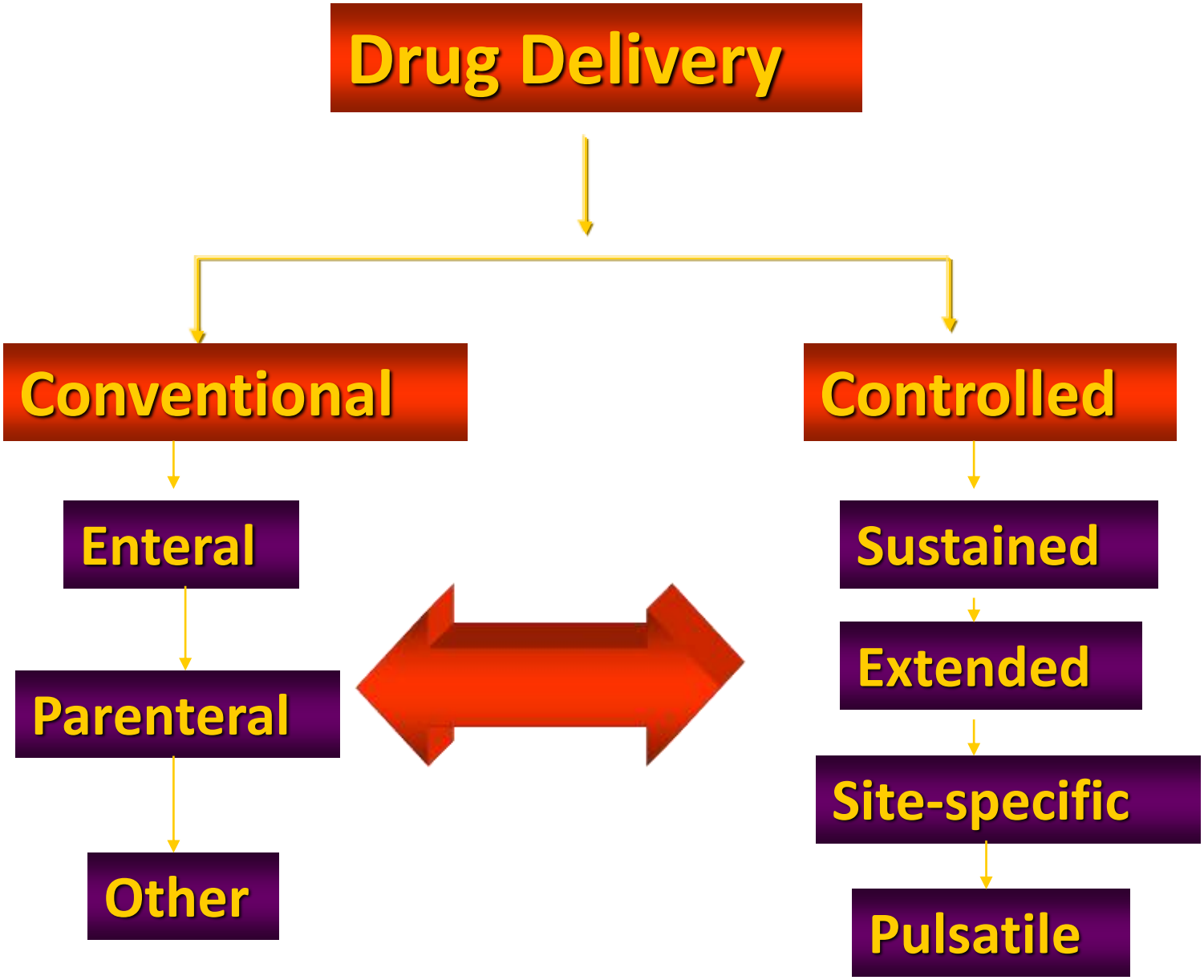
Zidovudine	Oral Solution
Didanosine	Powder (reconstitute with antacid)
Lamivudine	Oral Solution
Abacavir	Oral Solution
Nevirapine	Suspension
Efavirenz	Capsules (50 mg for 7 kg patient)
Ritonavir	Solution
Nelfinavir mesylate	Oral Powder (mix with foods)
Amprenavir	Oral Solution (propylene glycol)
Lopinavir/Ritonavir	Oral Solution
Acyclovir	Oral Suspension
Ribavirin	Powder for Inhalation Solution
Oseltamavir phosphate	Suspension

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
Conventional
Controlled
Enteral
Parenteral
Other
Sustained
Extended
Site-specific
Pulsatile

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

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**

Factors Influencing the Selection of the Delivery Route

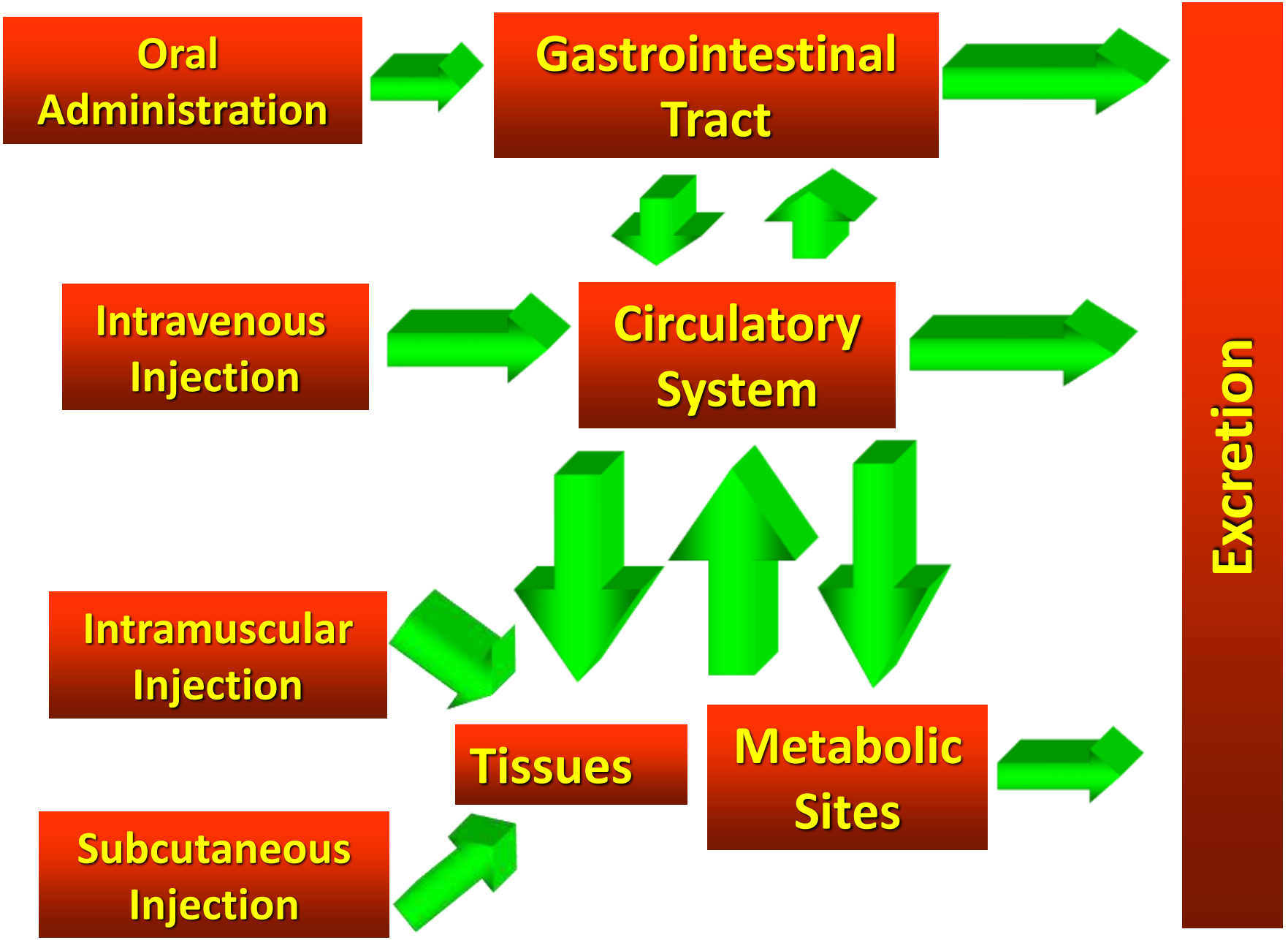
- **Solubility in aqueous solution (hydrophobicity/hydrophilicity)**
  - **pH**
  - **pKa - ionization**
  - **Temperature**
  - **Concentration**
  - **Crystalinity**
  - **Particle size**
  - **State of hydration**

Factors Influencing the Selection of the Delivery Route

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

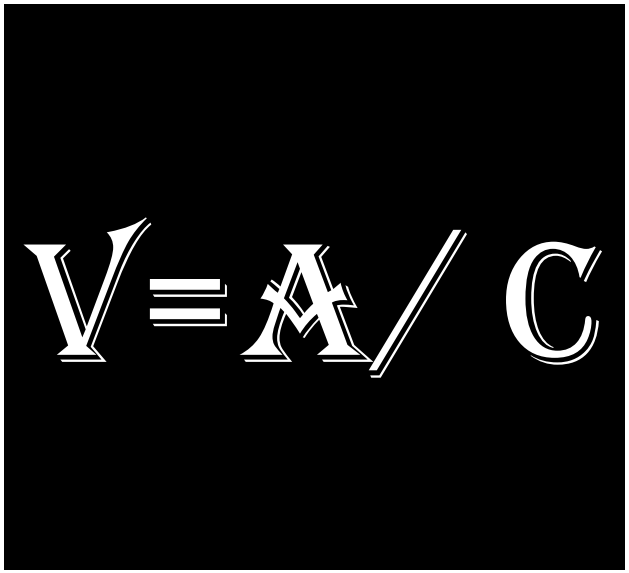
Manufacture of Classical Oral Delivery Systems

- **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


Oral Administration
Gastrointestinal Tract
Intravenous Injection
Circulatory System
Intramuscular Injection
Tissues
Metabolic Sites
Subcutaneous Injection
Excretion

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 = amount of drug in the body/Plasma drug concentration

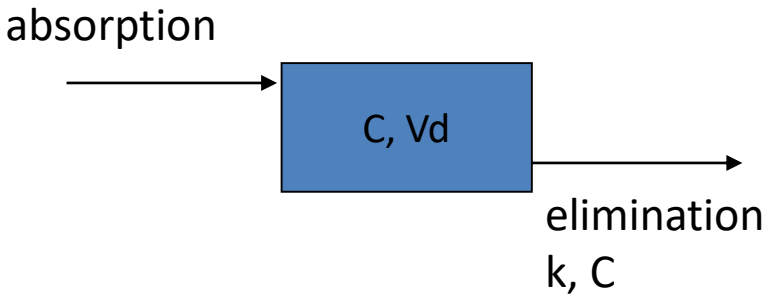


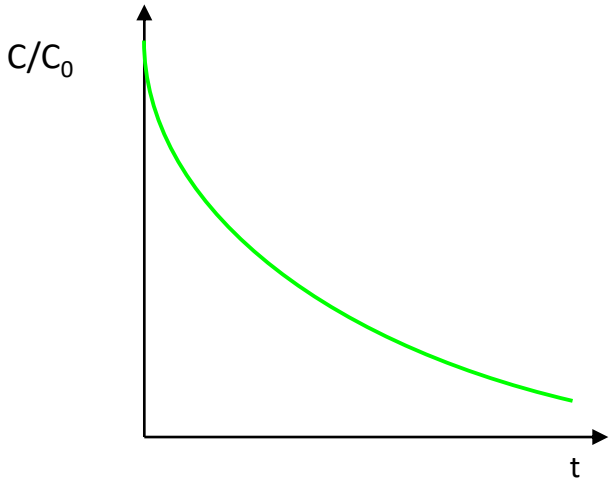
Mathematical Modeling of Drug Disposition

- Single compartment
- Single compartment with absorption
- Two compartments
- Two compartments with absorption

Single Compartment Model

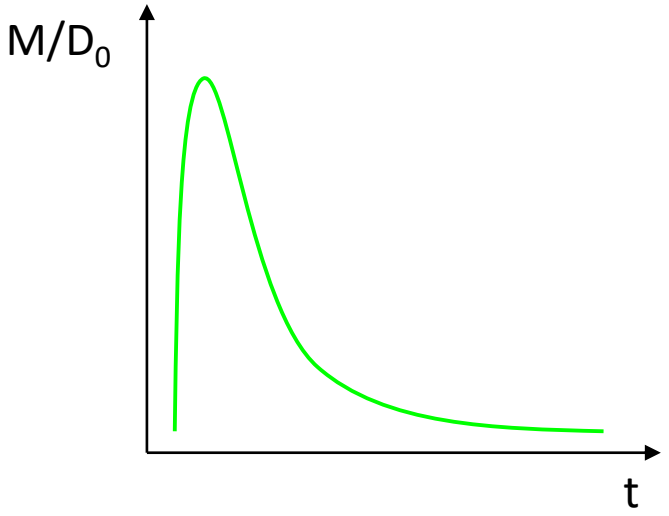
- Assumptions:
  - Body one compartment characterized by a volume of distribution (V_d)
  - Drug is confined to the plasma (small V)

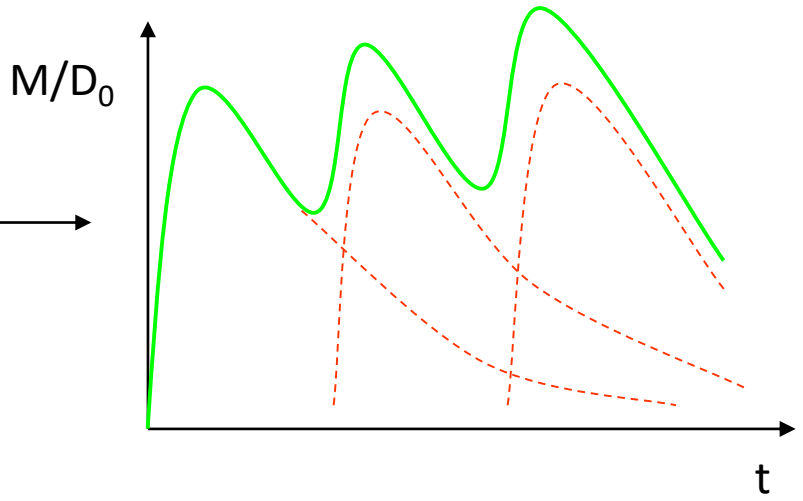




One-Compartment Model with Absorption

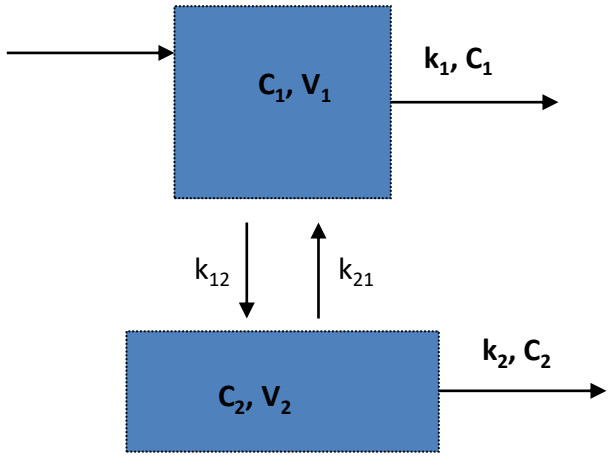
- Low absorption occurs
- Absorption is the rate-limiting step
- Slow absorption may represent drug entry through GI tract or leakage into circulation after SC injection
- Drugs require multiple doses to maintain drug concentration within therapeutic window

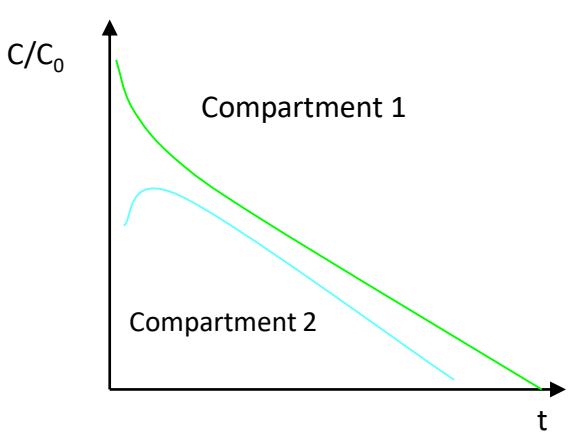




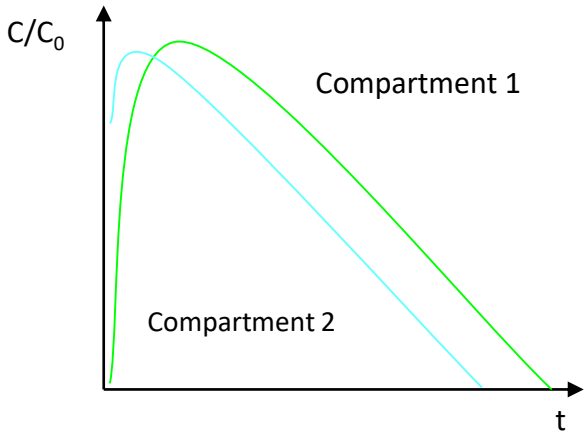
Two-Compartment Model

- 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

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 Bioavailabilty

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


thank you