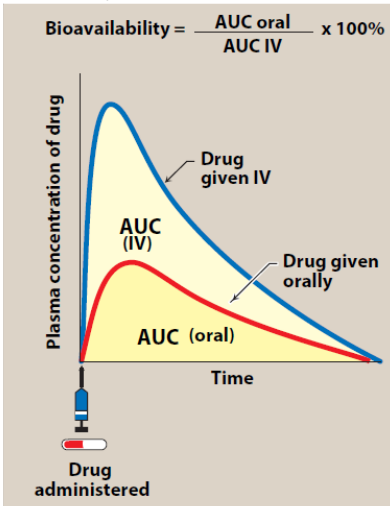
BIOAVAILABILITY

- **Definition**- Bioavailability is the rate and extent to which an administered drug by any route reaches the systemic circulation.
- For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.
- Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration because after I.V. administration, 100%of the drug rapidly enters the circulation
- **Determination of bioavailability:**
  - Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration with levels achieved by IV administration.
  - After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.



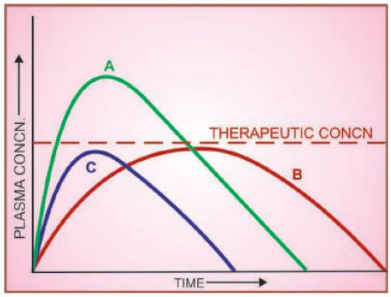


Figure: Plasma concentration-time curves depicting bioavailability differences between three formulations of a drug containing the same amount
Note that formulation *B* is more slowly absorbed than *A*, and though ultimately both are absorbed to the same extent (area under the curve same), *B* may not produce therapeutic effect after a single dose; however average blood levels may be similar with both A and B formulations when repeated doses are given; *C* is absorbed to a lesser extent—resulting in lower bioavailability

- **Factors that influence bioavailability:**
  - Orally administered drug undergoes first pass metabolism. This biotransformation along with physical and chemical characteristic of drugs , determine s the rate and extent to which the agent reaches the systematic circulation.

i) First-pass hepatic metabolism (presystemic elimination):

- When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism.
- First-pass metabolism by the intestine or liver limits the efficacy of many oral medications.
- For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual or transdermal, or intravenous route.
- Drugs with high first-pass metabolism should be given in such doses so that sufficient amount of drug reaches the site of action.For example, *propranolol* when given by the intravenous route requires much small doses compared to the oral dose

ii) Solubility of the drug:

- Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically(विडम्बना / विरोधाभास), drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, for a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

iii) Chemical instability:

- Some drugs, such as *penicillin G*, are unstable in the pH of gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

iv) Nature of the drug formulation:

- Drug absorption may be altered by factors unrelated to the chemistry of the drug.
- For example,
  - **i)** Particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.
  - **ii)** Sometimes, patients split or crush the tablets and open the capsule prior to administration which alter its absorption characteristics as follows:
    a) Crushing or opening enteric-coated tablets result in the drug to released too early in the stomach, and destroyed by stomach acid, or may irritate the stomach mucosa
    b) A sugar/film-coated dosage form is often used to help mask the unpleasant or bitter taste of some drugs (for example, *ibuprofen, quinine, cefuroxime axetil*, and *ciprofloxacin*).
    c) Coatings can also be added to photosensitive drugs to protect them from light (for example, *nifedipine*). Crushing an extended-release preparation may also change the drug release characteristics and result in releasing unintended large bolus of a drug.
    d) The consequence of crushing not only would lead to overdosing but also an increased risk of adverse effects. For example, extended release *nifedipine* may deliver the dose instantly and result in severe hypotension.
    e) Buccal or sublingual preparations should also not be altered. These medications are also not designed for absorption in the GI tract. This may result in reduced drug absorption and lack of efficacy.
  - **iii) Effect of excipient-**
    - Excipients are included in dosage forms to aid manufacture (for example, add bulk to the active drug used in extremely small quantities) or administration (to mask or lessen the unpleasant taste, for example, lactose and calcium lactate starch) or modulate absorption.
    - Most excipients have no direct pharmacological action; they are pharmacologically inert. However, in some cases physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drug products, and consequently their therapeutic efficacy and safety. Therefore, switching of brands of these medications may lead to changes in the bioavailability and hence may need dose adjustment with a change in the brand.

❖ **Bioequivalence and other types of equivalence**

- Two drug formulations are **bioequivalent** if they show comparable bioavailability and similar times to achieve peak blood concentrations.
- Two drug formulations are **therapeutically equivalent** if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that, drug products are bioequivalent and pharmaceutically equivalent.
- Bioequivalence can be an issue with generic versus branded/trade drugs. Although both generic and brand drugs may have the same amount of drug, the bioavailability of the drug may be different.