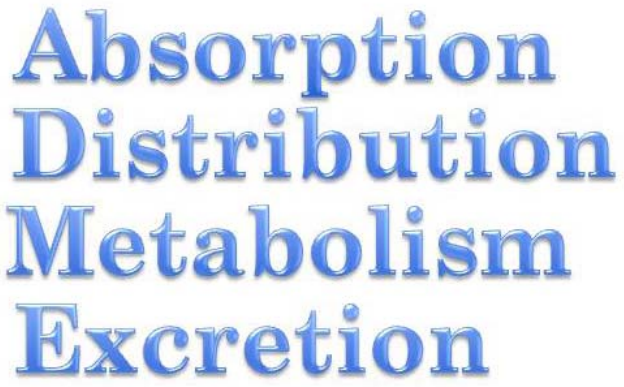
PHARMACOKINETICS – ABSORPTION

2.1 INTRODUCTION

Pharmacokinetics

- Is defined the study of drug movement in the body.
- Is what the body does to the drug.
- Pharmacokinetics is composed of four basic processes:



Absorption

- Drug absorption is the movement of the drug from the site of administration into the blood.
- The rate of absorption determines how quickly the drug effect will occur.
- The amount of drug absorption determines how intense the effect of the drug will be.

2.2 FACTORS AFFECTING ABSORPTION

1) Rate of Dissolution
2) Surface Area
3) Blood Flow
4) Lipid Solubility
5) pH Partitioning
6) Activity of Drug Transport Proteins

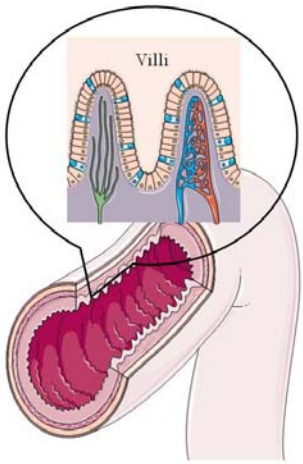
1) Rate of Dissolution

- Dissolution means dissolving in solution.
- Drugs must dissolve before they can be absorbed.
- Drugs with a fast rate of dissolution will have a faster onset of action than drugs with slow dissolution.
- The example to the right shows drugs placed in a liquid. Over time dissolution occurs and the drug

molecules are dissolved in the liquid. The same thing happens when we swallow a medication, the tablet undergoes disintegration and the medication dissolves in our stomach contents.

2) Surface Area

- Surface area is a major determinant of drug absorption.
- The larger the surface area, the faster drug absorption is.
- Which has the greater surface, the stomach or the small intestine?
- While the stomach has folds called rugae, the intestine has thousands of finger like projections called villi. The villi that line the intestine make the surface area very large.

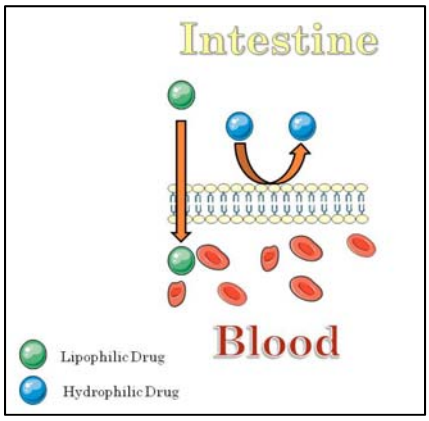


3) Blood Flow

- Drug absorption is fastest in areas with high blood flow.
- Areas with a high blood flow maintain a concentration gradient which drives absorption.
- Areas with low blood flow do not maintain as great of a concentration gradient.
- Exercise increases blood flow and can increase drug absorption.
- Blood flow is decreased in heart failure, severe hypotension, hypothermia and circulatory shock.

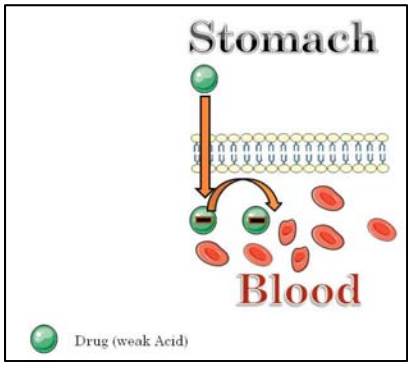
4) Lipid Solubility

- Drugs with high lipid solubility (i.e. lipophilic drugs) are absorbed more rapidly than water soluble (i.e. hydrophilic) drugs.
- Lipophilic drugs are able to cross the cell membrane whereas hydrophilic drugs can't.

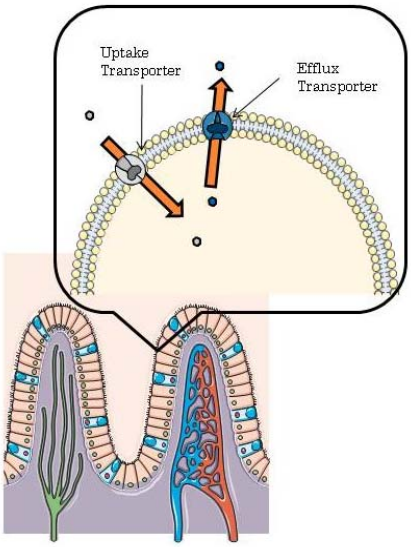


5) pH Partitioning

- Drug absorption is greater when there's a difference between the pH at the site of administration and the blood such that the drug is ionized in the blood.
- Remember the effect of pH dependent ionization from Module 1!



6) Activity of Drug Transport Proteins



- The rate and extent of drug absorption can be significantly impacted by drug transporters.
- Uptake drug transporters increase the absorption of drugs.
- Efflux drug transporters decrease the absorption of drugs.

2.3 ROUTES OF ADMINISTRATION

- There are 8 major routes of drug administration summarized below.

1) Oral (PO = *per os* which is latin for by mouth)
2) Sublingual
3) Transdermal
4) Rectal
5) Intravenous (IV)
6) Subcutaneous (SubQ or SC)
7) Intramuscular (IM)
8) Pulmonary

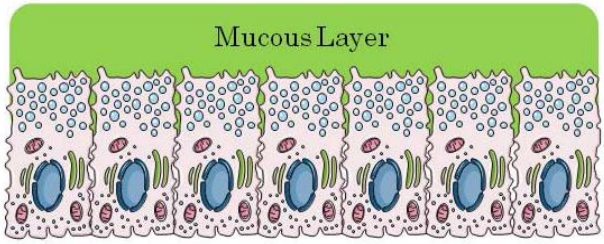
- Routes of administration are often referred to as enteral or parenteral.
- Enteral – Routes of administration that involve the gastrointestinal tract.
- Parenteral – Routes of administration that do not involve the gastrointestinal tract.

Enteral	Parenteral	Other
Oral	Intravenous	Sublingual
Rectal	Intramuscular	Transdermal
	Subcutaneous	Pulmonary

1) Oral Absorption

Intestine vs Stomach

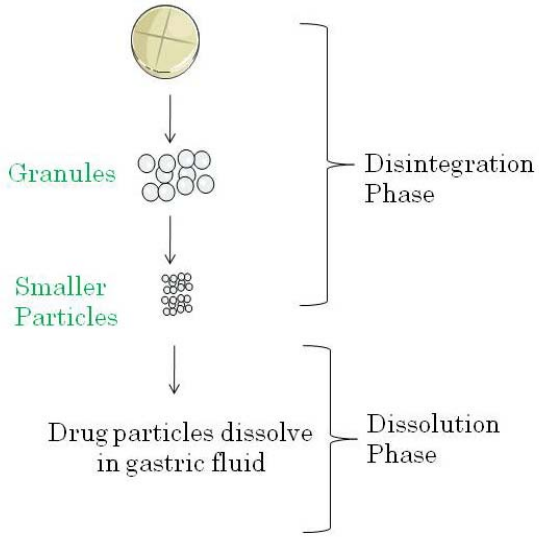
- Earlier we discussed the impact of surface area on drug absorption and determined that the intestine has a much larger surface area than the stomach, therefore drug absorption would be greater in the intestine than the stomach.
- What about drugs that are weak acids, wouldn't they be better absorbed in the stomach?
- Based on the pH effects weakly acidic drugs should be better absorbed in the acidic environment of the stomach because they would unionized.
- However, the surface area of the stomach is small and the stomach is covered with a thick layer of mucous.



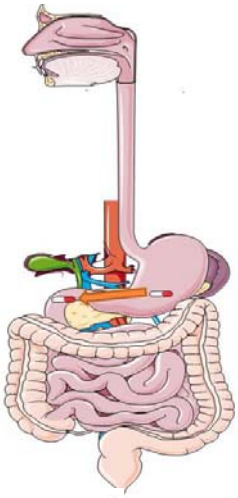
- Therefore the rate of drug absorption in the intestine will be greater than the stomach, even if the drug is ionized!
- The bottom line is for most drugs, oral absorption is greatest in the intestine.

Pharmaceutical Phase

- The pharmaceutical phase occurs after the patient swallows a tablet.
- It involves the disintegration of the tablet and the dissolution of the drug.
- If the drug does not completely disintegrate or does not go into solution, absorption is reduced.



Gastric Emptying

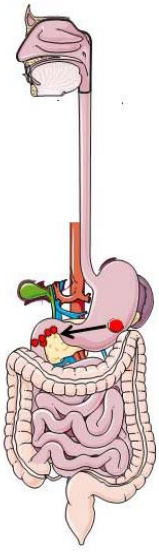


- Gastric emptying is quite simply the movement of the stomach contents into the intestine.
- Since the rate of drug absorption is greater in the intestine, things that increase gastric emptying also increase the rate of drug absorption.

Factors Affecting Gastric Emptying

Increase Gastric Emptying	Decrease Gastric Emptying
Taking medications on an empty stomach	High fat meal
Taking medications with cold water	Heavy exercise
Lying down on the right side	Lying down on the left side
High osmolality feeding (tube feeding)	Taking a drug that inhibits the vagus nerve (i.e. anticholinergic drugs)
Taking a prokinetic drug (a drug that increases GI motility)	

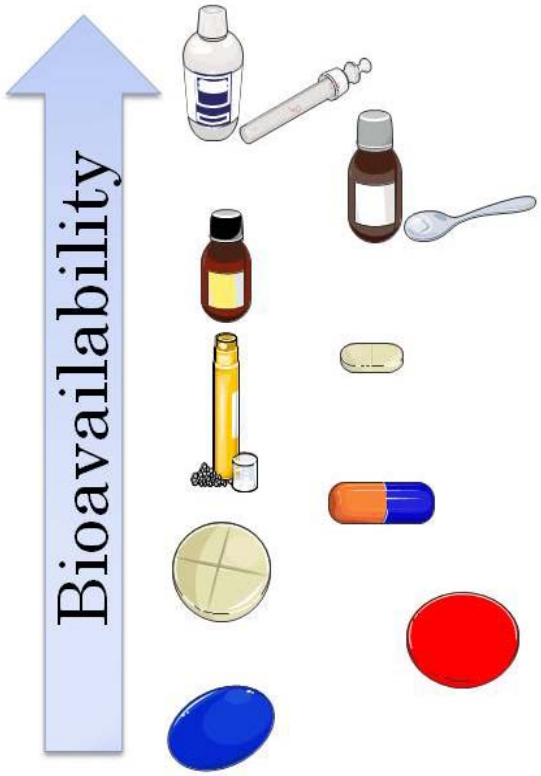
Enteric Coating



- Drugs with enteric coating are covered with a special coating that prevents their dissolution in the acidic environment of the stomach.
- Once the drug passes into the more alkaline duodenum, the enteric coating dissolves.

Bioavailability

- Bioavailability is the fraction of a dose of drug that reaches the systemic circulation unchanged.
- Bioavailability can be influenced by:
    1) Drug formulation
    2) Route of Administration
    3) Degree of Metabolism



Aqueous Solution

Syrup

Suspension

Chewable Tablet

Granules

Capsules

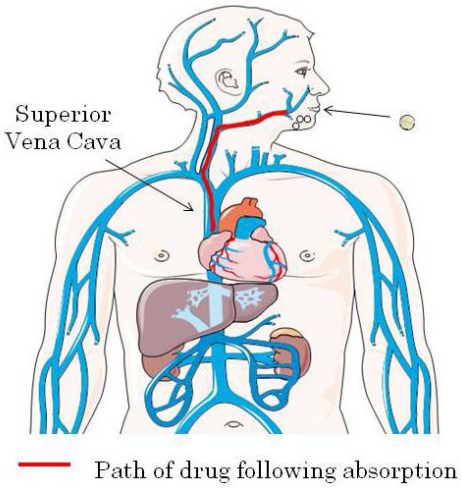
Compressed Tablet

Enteric Coated Tablets

Time Release Capsules

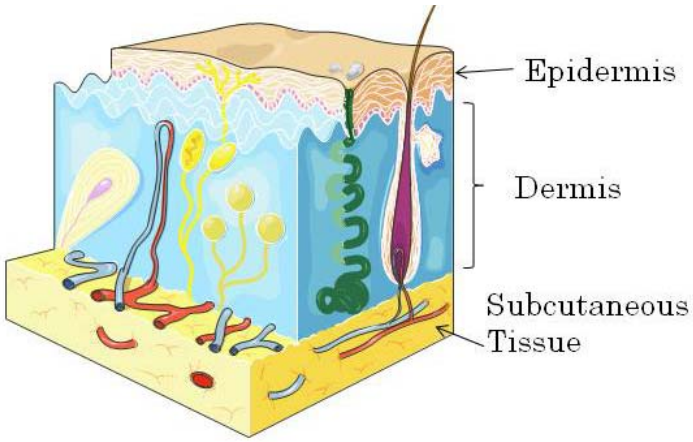
2) Sublingual

- Involves placing a drug under the tongue.
- The drug dissolves and is absorbed across the oral mucosa.
- Venous drainage from the oral mucosa is to the superior vena cava. Superior vena cava takes blood to the heart.
- Drugs administered sublingually avoid first pass metabolism through the liver.
- In order to be absorbed drugs must be lipophilic and uncharged.



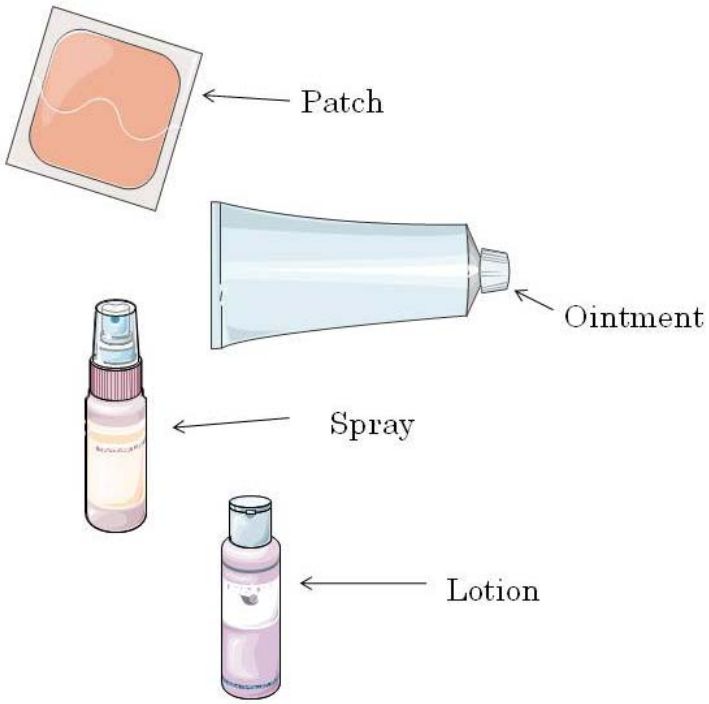
3) Transdermal

- Not all drugs penetrate the skin.
- The epidermis provides a lipid barrier, therefore drugs must be lipophilic enough to penetrate the skin.
- Drugs must also be relatively hydrophilic in order to dissolve in the extracellular fluid.
- Ideal transdermal preparations have some degree of lipophilicity and some degree of hydrophilicity and are usually small (< 600 Da) molecules.



Transdermal Preparations

- Transdermal drugs are typically administered as patches, ointments, sprays or lotions.
- Transdermal administration provides constant plasma drug levels with minimal peaks and troughs.
- Tolerance may develop unless drug-free period's are enforced. Typically patches are removed for 6 – 10 hours per day to avoid tolerance.

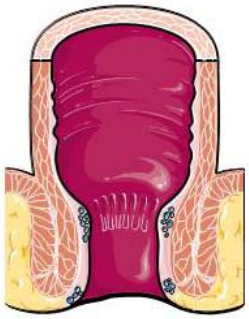


Factors Affecting Transdermal Absorption

1) **Thickness of the skin** – Transdermal absorption is inversely proportional to skin thickness.
2) **Hydration** – Transdermal absorption is increased when the skin is well hydrated.
3) **Hair follicles** – Provide routes for drugs to bypass the barrier function of the epidermis. In general the greater the number of hair follicles, the greater the transdermal absorption is.
4) **Application Area** – The greater the application area, the greater the transdermal absorption.
5) **Integrity of the barrier** – In conditions such as psoriasis, burned or abraded skin, transdermal absorption is increased.

4) Rectal

- Useful when the patient is unconscious or vomiting.
- Approximately 50% of rectally administered drugs bypass the liver (an important site for drug metabolism).
- Administration: The drug is inserted into the rectum as a suppository. The suppository dissolves and the drug crosses the rectal mucosa into the blood.
- Disadvantages include incomplete absorption and some drugs may irritate the rectal mucosa.



Rectum

Rectal suppository

5) Intravenous (IV)

- Drug is injected directly into a peripheral vein.
- Most commonly used veins are those on the back of the hand or the median cubital vein at the elbow although any visible vein may be used.
- Intravenous drugs can be given as a bolus or by an IV drip.
- In IV bolus a single dose is administered over a short time period.
- In an IV drip a drug is administered under continuous infusion over a prolonged period. Drugs are typically diluted in a "vehicle" such as saline in an IV bag.

IV Bolus

IV Drip

Advantages

- No barriers to absorption, bioavailability is 100%.
- Allows precise control of the drug dosage and duration of action.
- Allows administration of poorly soluble drugs that must be diluted in a large volume.
- Allows the injection of drugs that are irritants (i.e. many chemotherapeutic drugs) as they can be injected slowly so they are diluted in the blood.

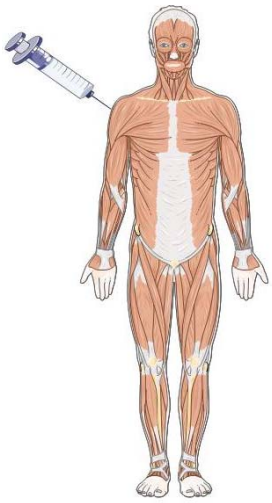
Disadvantages

- Expensive, invasive and inconvenient.
- Drug cannot be removed once injected.
- Risk of infection and fluid overload.
- Risk of injecting wrong formulation (IM formulation sometimes injected IV by accident).

6) Subcutaneous

- Drug is injected beneath the skin into the subcutaneous tissue.
- The only barrier to absorption is the capillary wall.
- Irritant drugs must not be injected subcutaneously as this will cause severe pain and/or tissue sloughing.
- The primary determinants of rate of absorption are blood flow and water solubility.

7) Intramuscular (IM)



- Drug is injected directly into muscle tissue.
- Absorption is determined by the ability of the drug to pass through fenestrations in the capillary wall.
- The primary determinants of rate of absorption are blood flow and water solubility.

Advantages:

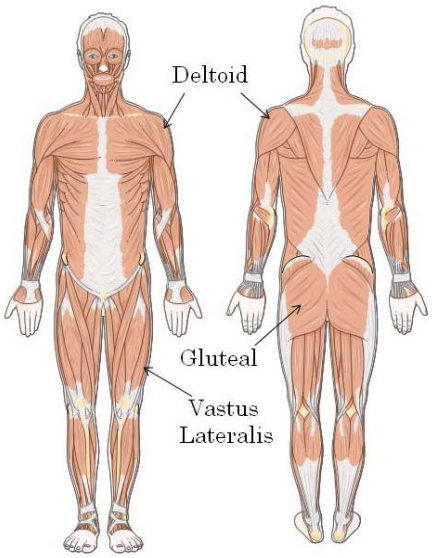
1. Can be used for poorly soluble drugs.
2. Can use it to administer depot preparations (preparations in which the drug is absorbed slowly over time).

Disadvantages:

1. Pain/discomfort
2. May cause local tissue and/or nerve damage if the injection is done improperly.

Factors Affecting Intramuscular Absorption

- Blood flow is different depending on which muscle is used for injection. In general blood flow is deltoid > vastus lateralis> gluteal.
- Exercise increases blood flow and may therefore increase absorption for IM drugs.
- Blood flow may be decreased in heart failure, severe hypotension and hypothermia.



8) Pulmonary

- Gaseous and volatile drugs can be inhaled and absorbed into the blood through the pulmonary epithelium.
- Absorption is very rapid (almost instantaneous) due to the large surface area of the lung.
- In the case of pulmonary disease (i.e. asthma), the drug is delivered to its site of action which is a major advantage.
- Drugs such as general anaesthetics used in surgery are also often administered by the pulmonary route of administration.