The Oral Route of Drug Administration

Objectives:

1. Understand the Oral route of drug administration, its advantages and disadvantages.
2. Understand the mechanisms by which drugs may be absorbed.
3. Understand the factors that affect drug absorption through the oral route.
4. Predict whether, and to what extent, a patient's actions/ behavior, pathology or co-administered drugs will affect drug absorption.

Reading Assignment:

The following pages are your reading for the next topic: **Oral Route of Drug Administration.**

1. Handout supplemented on **Oral Route of Drug Administration**.

2. Ansel Pharmaceutical Dosage Forms and Drug Delivery P.186 Table 5.3 "Some Factors that influence Bioavailability of Oral Drugs".

3. Ansel Pharmaceutical Dosage Forms and Drug Delivery Pages 188 -192 "Oral Route"to "Rectal Route".

You need to focus on the following for the iRAT

1. **What is the oral route of administration? What are the dosage forms applicable to this route?**
2. **Advantages and disadvantages of the oral route.**
3. **What is the fate of drug in the body after ingestion?**
4. **Factors affecting drug absorption through the oral route.**

The Oral Route of Drug Administration

LEARNING OBJECTIVES

1. Understand the Oral route of drug administration.
2. Understand the mechanisms by which drugs may be absorbed.
3. Understand the factors that affect drug absorption through the oral route
4. Understand how a patient's actions/ behavior, pathology or co-administered drugs will affect drug absorption.

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****(Some material in this handout was adopted from Dr. Pather's handout on Oral Route)*

The Gastrointestinal Tract (GI tract) is a hollow tract made of several organs.

1) **Esophagus:** once food in the mouth is swallowed it is pushed into the esophagus, a muscular tube that connects the mouth to the stomach, via peristalsis i.e involuntary muscle contraction food travels down the tube to the stomach.
2) **Stomach** the function of the stomach is to store the food, mix it with digestive fluids of GI to form a slurry called chyme, that chyme is pushed into the small intestine for further digestion.
   The stomach is made up of 3 basic parts: the fundus, body and antrum. Food enters the stomach and is stored in the fundus and body. This part of the stomach can swell owing to the minimal muscular activities of its walls. A layer of mucus consisting of mucopolysaccharides lines the epithelial cell surface, it protects the stomach and keeps it lubricated. About 2L of gastric fluid is secreted by gastric glands. This fluid is acidic due to a high content of HCl. The antrum is the major site of mixing motions owing to its muscular activity; capable of accomplishing gastric emptying.

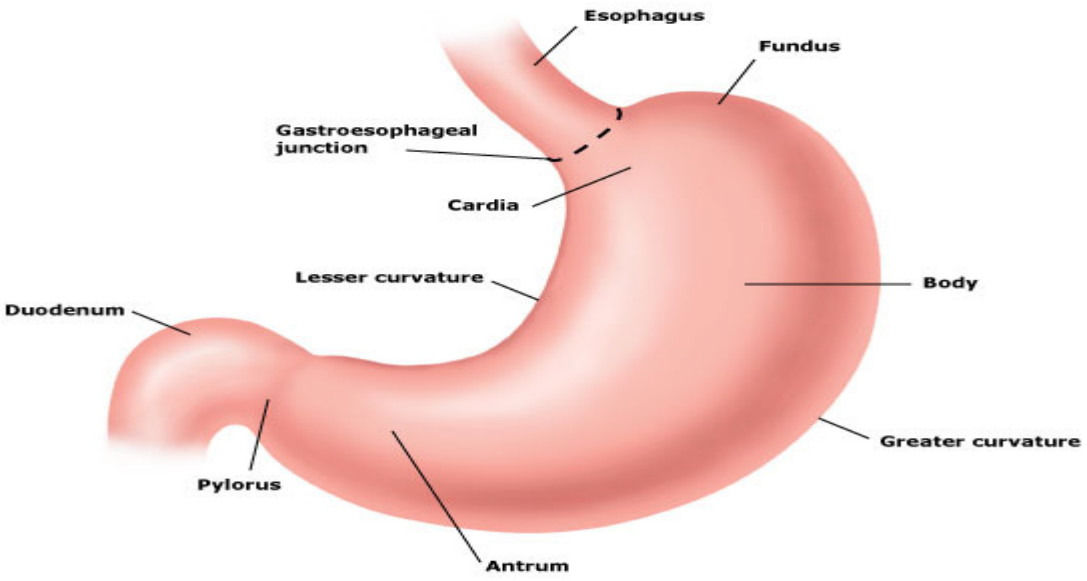

Figure: 1 Diagram of the stomach

http://www.aboutcancer.com/Parts_of_stomach_utd.jpg

3) **The Small Intestine:** In the intestine the chyme is mixed with the juices of the pancreas, intestine and liver for further digestion. The digested nutrients are absorbed through the walls of the small intestine and into to the bloodstream. Owing to its unique structure the small intestine represents the major part of absorption in the GIT.

   The small intestine a convoluted tube has a large surface area unique structure which makes it ideal for absorption. The large surface area is due to the following unique structures:

1. Finger-like projections known as villi line the internal surface.
2. Projecting from the villi are fine structures, the microvilli.
   Both these structures give the small intestine a large surface area.

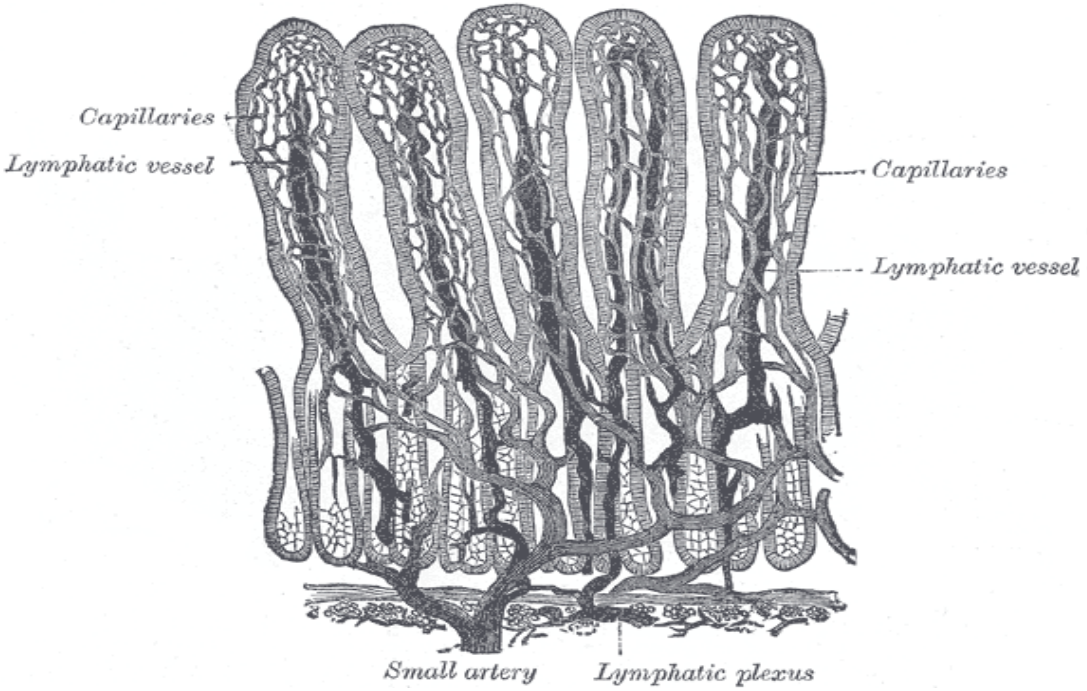

Figure 2: Villi of small intestine, showing blood vessels and lymphatic vessels.
[Henry Gray (1825–1861). Anatomy of the Human Body. 1918.]

3. ***The Large Intestine:*** the waste product of the digestive process passes through the large intestine. The large intestine has two main functions:
   i. The large intestine absorbs water and any nutrients and forms the feces***.***
   ii. In the large intestine the feces are stored in the rectum and are released outside the body during a bowl movement.

Routes of Administration:

There are two routes of Administration. The ***enteral route and the parenteral route.*** The term "enteral" refers to the "enteron" or gastrointestinal tract (GIT). Any drug that is absorbed through the GIT has entered the body via the enteral route this includes oral, sublingual, buccal and Rectal. While the term parenteral signifies all other route other than enteral, examples are parenteral dosage form such as intravenous (IV), Intramuscular (IM) and Subcutaneous (SQ).

Drugs are more frequently administered through the oral route. Drugs taken orally are mostly intended to be swallowed except for few which are intended to dissolve in the mouth such as buccal or sublingual.

Drugs swallowed are to exert their effect systemically while few exert their effect locally such as the use of antacids. In the oral route the drug is swallowed passes through the Gastrointestinal tract GI tract, first, it passes into the stomach and then the small intestine where it is absorbed into the blood stream. The blood carries the drug to the liver where a portion of it is degraded. This is termed "First Pass Effect". The remaining intact drug passes into the general circulation and is carried to the site of action where it reacts with receptors to exert a pharmacological response.

What are the dosage forms applicable to this route?
Tablets, capsules, solutions, syrups, elixirs, suspensions, magmas, gels and powders.
Oral route is the most convenient route for access to the systemic circulation.

Limitations of Oral route:

1. To be avoided when patient is
    a. Gastrointestinal intolerance: Vomiting and nausea
    b. Convulsion
    c. When Rapid onset is desired in an Emergency
    d. Patients who have difficulty swallowing. e.g Pediatric and geriatric patients.

Advantages of Oral route:

1. Can be self administered.
2. Economic (cheap to manufacture).
3. Mostly stable on storage.
4. Easy to transport.

Disadvantages of Oral Route:

1. Delayed onset.
2. Taste of the drug can present a problem. How to overcome?
3. Drug may be degraded in stomach in acidic media. How to avoid?
4. Poorly soluble drugs may have limited absorption.
5. Absorption may vary from patient to patient or in the same patient. depending on if food was taken with the drug and the nature of meal.
6. Drugs that have short absorption window. (only a small part of the GIT is capable of absorbing the drug).
7. The drug may be susceptible to enzyme degradation in the GIT.

Pathways of drug movement and modification in the body:

What is the fate of the drug in the body once it gets ingested ?

First, Absorption: drug absorption from the site of administration allows the entry of the drug into the plasma.

Second, Distribution: where drug may reversibly leave the blood stream and distribute into tissues.

Third, Metabolism: the drug may be metabolized by the liver, kidney or other tissues.

Finally, Elimination: the drug and its metabolites are eliminated from the body in urine, bile or feces.

Absorption:

Absorption is the process by which a drug leaves it's site of administration/application into the extracellular compartment of the body.

How are drugs absorbed and what factors affect their absorption? Assuming the use of immediate release product we expect a rapid and complete absorption in the blood stream.

Factors affecting drug absorption:

1. Physiological properties
2. Physicochemical properties of the drug molecule e.g lipid solubility.
3. Dosage form characteristics and Formulation Factors (ingredients)

1. Physiological factors affecting oral absorption (outline)

A. Passage of drugs across membranes
   i. Active transport
   ii. Facilitated diffusion
   iii. Passive diffusion

B. Gastrointestinal physiology
   i. Characteristics of GIT physiology and drug absorption
   ii. Gastric emptying time and motility
   iii. Malabsorption or pathologic condition.

The biologic membrane is mainly a lipid bilayer in nature that contains small aqueous channels or pores and protein drifting between the lipids. These proteins act as carriers. This model is called the Fluid Mosaic model.

A. Passage of Drugs Across Membranes:

i. Active transport or carrier mediated transport:

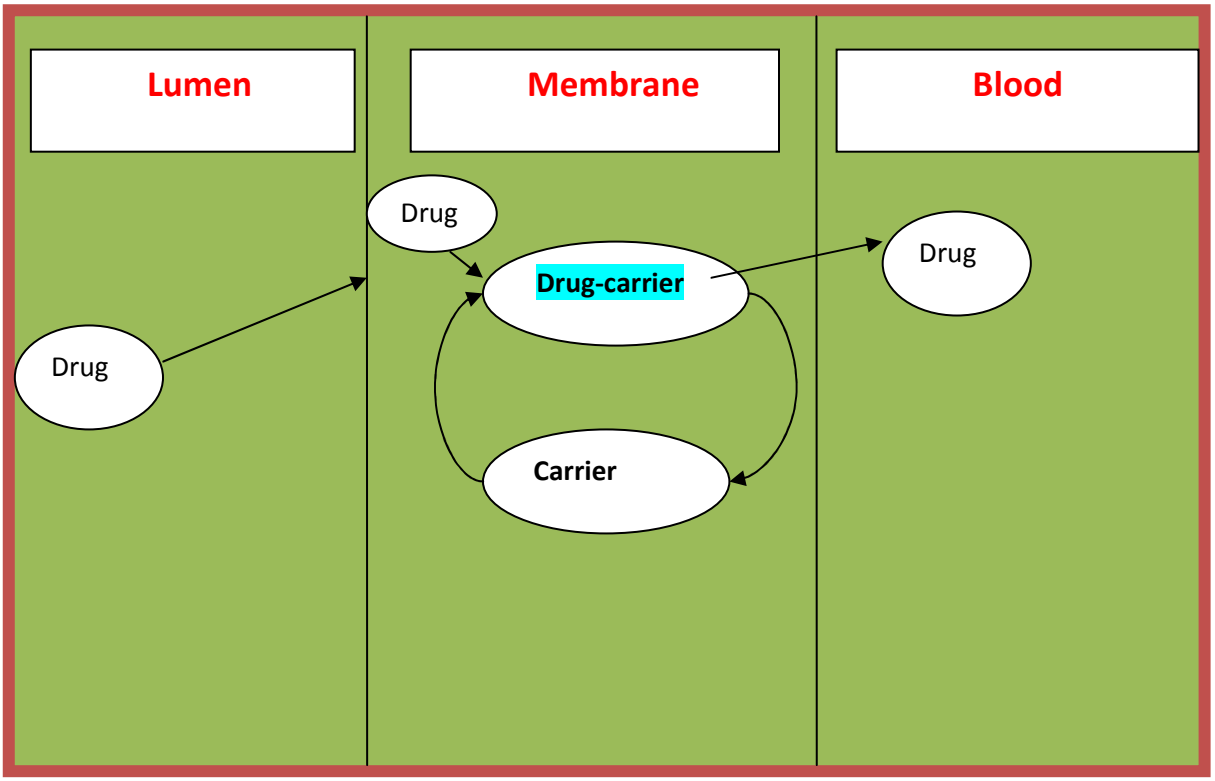

Fig: 3: Carrier-Mediated Transport Process

Transporting particular compounds; for example, glucose and amino acids requires specialized mechanisms. Some drugs can participate in this process; e.g. 5-fluorouracil. Active transport requires a carrier molecule and a form of energy.

- This process can be saturated.
- Transport may proceed against a concentration gradient.
- There is a possibility of competitive inhibition.

ii. Facilitated diffusion

A drug carrier is required but not energy. e.g. vitamin B12 transport.

- This process can be saturated.
- Transport is not against a concentration gradient.

iii. Passive diffusion:

Most drugs cross biologic membranes by passive diffusion. Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side. Drug diffuses across the membrane in an attempt to equalize the drug concentration on both sides of the membrane. If the drug partitions into the lipid membrane a concentration gradient can be established. We will discuss diffusion in greater detail in a different lecture.

B. Gastrointestinal Physiology:

i. Characteristics of GIT physiology and drug absorption

Organs	pH	Surface Area	Transit Time	By-pass liver
Stomach	1.5-3.5	small	30 min (liquid) - 120 min (solid food)	no
Small Intestine	6 -7	very large 10 - 14 ft, 80 cm^2 /cm	about 3 hours	no
Large Intestine	7-8	not very large 4 - 5 ft	long, up to 24 hr	lower colon, rectum yes

ii. Gastric emptying:

Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption. There is a good correlation between stomach emptying time and peak plasma concentration for drugs. The faster the stomach emptying (i.e shorter stomach emptying time) the higher the plasma concentration. Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.

Factors Affecting Gastric Emptying

Volume of Ingested Material	A large meal hastens stomach emptying. Why? Stomach distension causes faster emptying	Increase
Type of Meal	Fatty food	Decrease
	Carbohydrate	Decrease
Temperature of Food	Increased temperature	Increase
Drugs	Anticholinergics (e.g. atropine), Narcotic (e.g. morphine), Analgesic (e.g. aspirin)	Decrease
	Metoclopramide, Domperidone, Erythromycin, Bethanchol	Increase

iii. Malabsorption

Malabsorption is any disorder with impaired absorption of fat, carbohydrate, proteins and vitamins. Drug induced malabsorption has been observed after administration of neomycin, phenytoin and anticancer agents.

Factor	Mechanism	Effect on Absoprtion
Anticancer agent/Phenytoin	Damage mucosa that serve as barrier to large molecules	Enhance absorption
Surgical resection of small intestine	Reduce area of absorption	Reduce Absorption
Disease in bowl	Different	May reduce or enhance

2. Physicochemical properties of the drug substance:

A. Lipid or water solubility of drugs
B. pH and pK_a
C. Crystalline or amorphous
D. Salt form

A. Lipid and water solubility of drugs:

The cell surface is lipid in nature. A drug in aqueous solution experiences attractive forces from the water molecules (to keep it in solution) and also from the lipid cell membrane. The **balance** between the lipid attraction and the hydrophilic attraction of the water (hydrogen bonding) will determine the extent that the drug leaves the water phase and will dissolve in the lipid cell membrane and then be absorbed into the cell. The best parameter to correlate between water and lipid solubility is partition coefficient.

Partition coefficient ($K_{o/w}$) = $[L]_{conc} / [W]_{conc}$, where $[L]_{conc}$ is the concentration of the drug in lipid phase, $[W]_{conc}$ is the concentration of the drug in aqueous phase. The higher ($K_{o/w}$) value, the more absorption is observed. The biological membrane is a lipid bilayer.

Some drugs are poorly absorbed after oral administration even though they are un-ionized in small intestine. Their low lipid solubility may be the reason.

B. pH and pKa:

For a drug to cross a membrane barrier it must normally be soluble in the lipid material of the membrane to get into membrane and it has to be soluble in the aqueous phase as well to get out of the membrane. Many drugs have polar and non-polar characteristics or are weak acids or bases. For drugs which are weak acids or bases the pKa of the drug, the pH of the GI tract fluid and the pH of the blood stream will control the solubility of the drug and thereby the rate of absorption through the membranes lining the GI tract.

A drug either a weak base or a weak acid, if it is ionized it will not be able to get through the lipid membrane, but only when it is un-ionized it has a higher lipid solubility and it can partition into the lipid bilayer of the membrane. This is expressed in the following equation; **The Henderson Hasselbach Equation.**

Henderson - Hasselbach Equation – For weak Acids

$$\boldsymbol{pH = pKa + \log \frac{(ionized)}{(unionized)}}$$

Where, (ionized)=(salt) and (unionized)=(acid)

Henderson - Hasselbach Equation –For weak bases:

$$\boldsymbol{pH = pKa + \log \frac{(unionized}{(\mathbf{ionized})}}$$

Where, (unionized)=(base) and (ionized)=(salt)

With a weak acid, as the pH of the solution is lowered, the fraction of the drug in the un-ionized state increases. Similarly with a weak base, as the pH of the solution is raised, the fraction of the drug in the unionized state increases.
In other words:

	Weak acid	**Weak base**
If the pH is less than the pKa	Un-ionized	ionized
If the pH is greater than the pKa	ionized	un-ionized

Problem:

ASA has a pKa of 3.5. At a gastric pH of 2, what percentage of the drug would exist in the ionized and unionized? Would absorption be expected for this drug in the stomach at pH of 2?

Answer:

$$pH = pKa + \log\frac{(ionized)}{(unionized)}$$

$$2 = 3.5 + \log\frac{(ionized)}{(unionized)}$$ Hint : take inverse log to solve

$$-1.5 = \log\frac{(ionized)}{(unionized)}$$

$$0.03162 = \frac{ionized}{unionized}$$

$$(ionized) = 0.03162(unionized)$$

We know (ionized) +(unionized)= 1 Substitute 0.03162(unionized) for ionized

0.03162(unionized)+(unionized)= 1 = 0.03162 X+ X= 1 solve for X, X=unionized

(unionized)= 96.9% and (ionized)= 3.1%

Yes, absorption is expected as the drug exists primarily in the unionized.

Note: expect to solve similar problems in class for applications. Not in iRAT.

C. Crystalline or amorphous:

Some drugs exist in a number of crystal forms or polymorphs. These different forms may well have different solubility properties and thus different dissolution characteristics. This will be discussed in greater detail in another lecture.

D. Salt Form:

Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base, therefore if the drug can be given as a salt the solubility can be increased and we should have improved dissolution. One example is Penicillin V.

3. Dosage form characteristics and Formulation Factors (ingredients)

This section will be dealt with later in greater detail when discussing each dosage form.

1. Disintegration rate (tablets).
2. Dissolution time of drug in dosage form.
3. Product age and storage conditions.
4. Pharmaceutical ingredients such as fillers, binders, lubricants, disintegrating agents.