Pharmacokinetics

ABSORPTION II

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- **Sources**
- **Lippincott Illustrated Reviews: Pharmacology 7th Edition**
- **Katzung ; Basic & Clinical Pharmacology 14th Edition**
- **Bennett & Brown ; Clinical pharmacology 11th edition**
- **Essentials of Medical Pharmacology; Lafi 09**

The Nature of Drugs

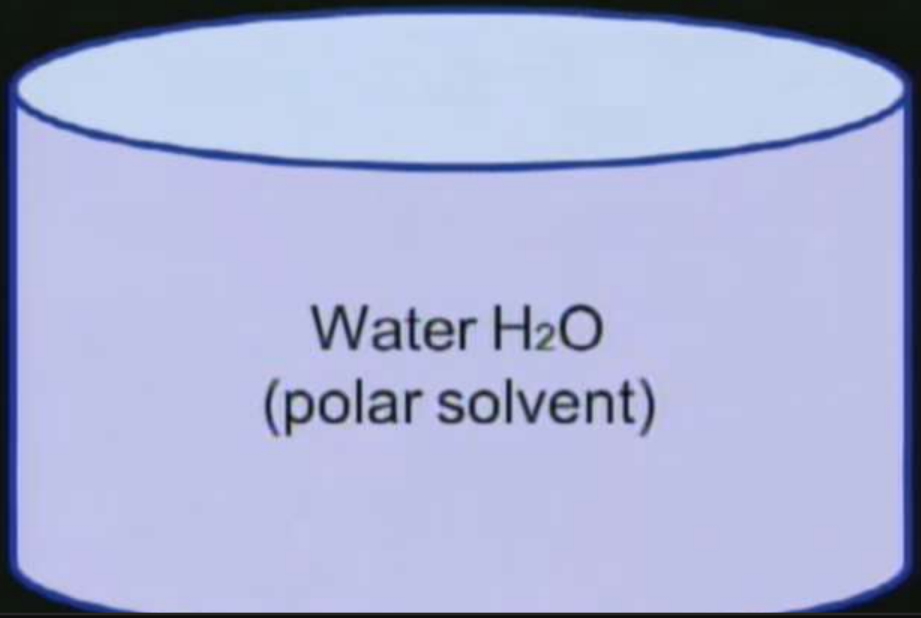
- Most drugs are:
  - –weak acids
  - –weak bases

Weak

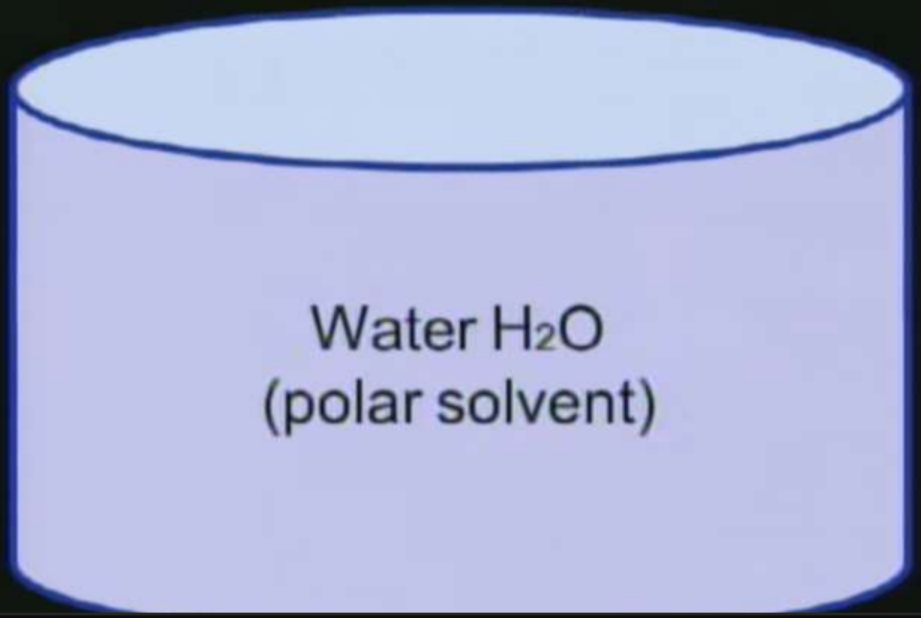
- Weak means incomplete dissociation in water

Aspirin

WEAK ACID

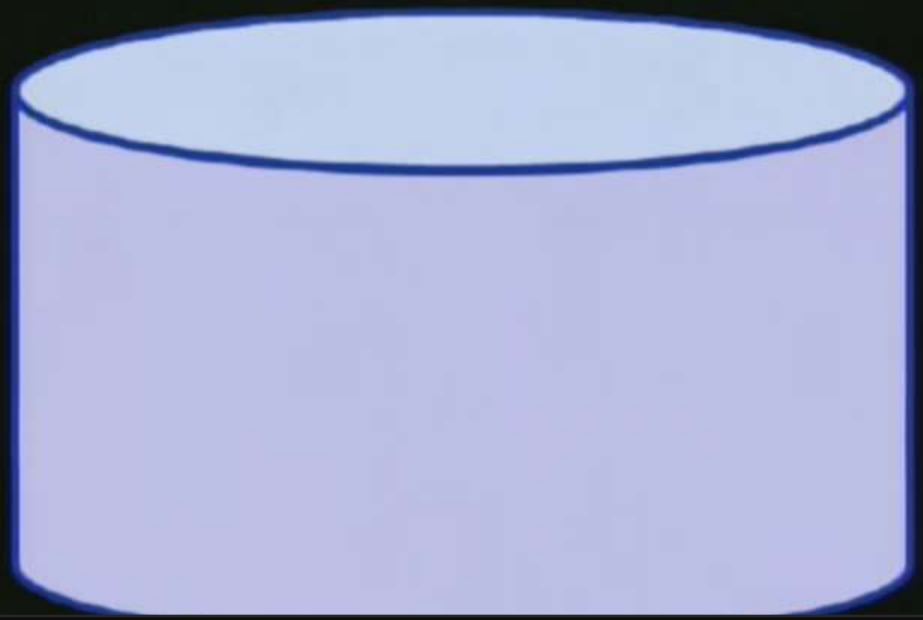


Aspirin R - COOH
White powder

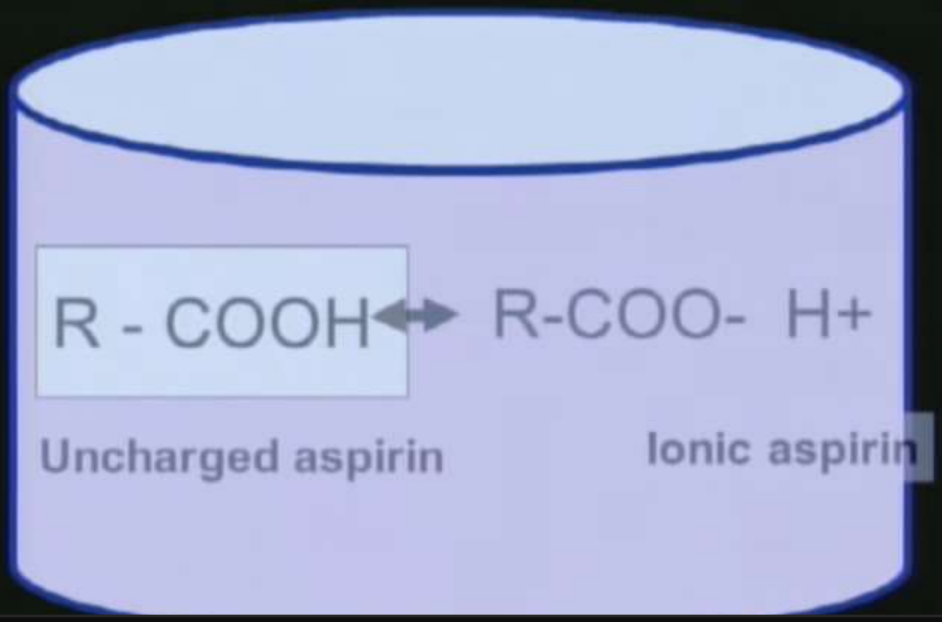


Aspirin

R - COOH

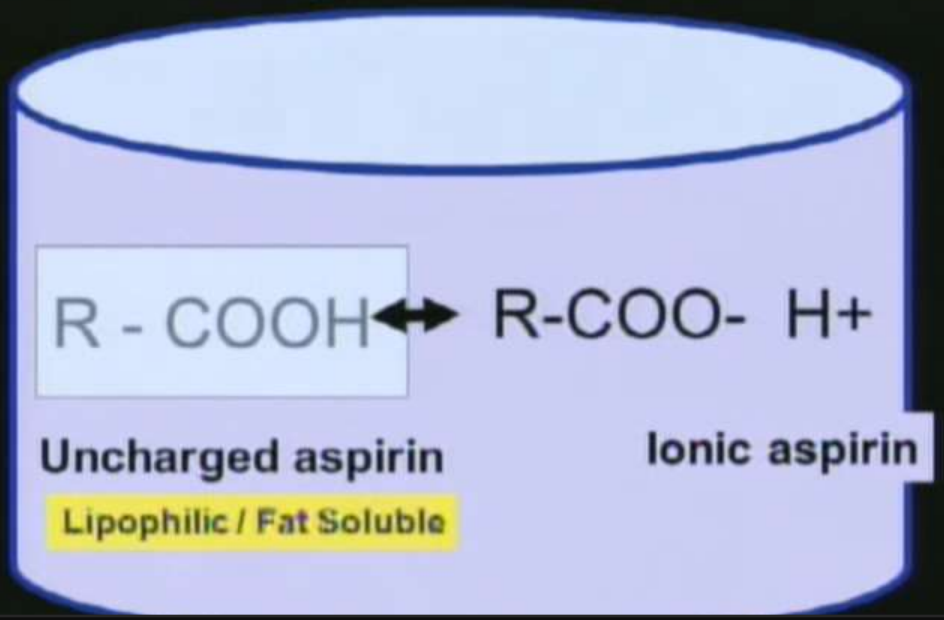


Aspirin



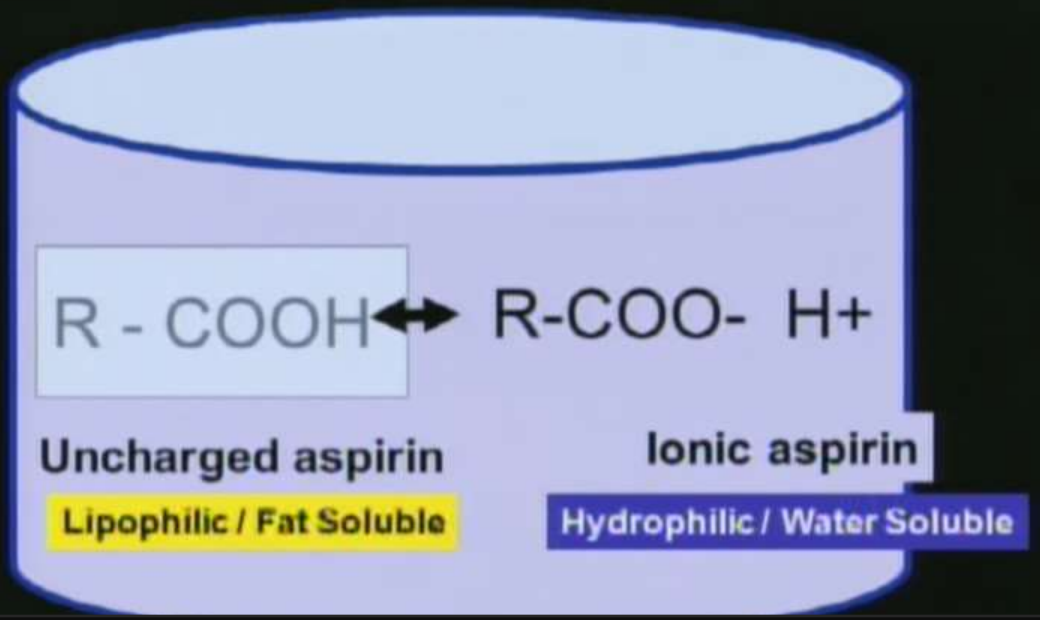
Aspirin


FOCUS

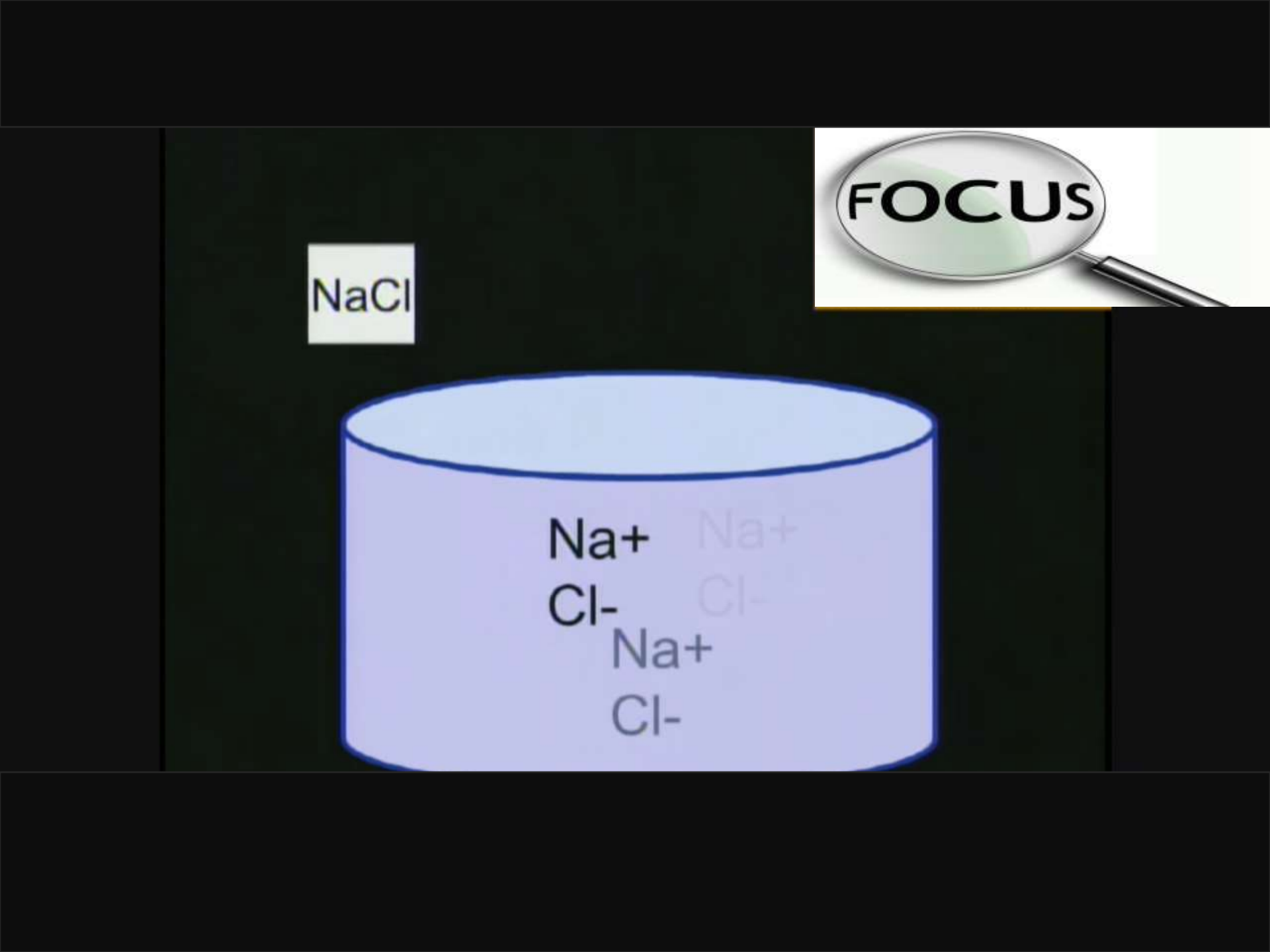

R - COOH
R-COO- H+
Uncharged aspirin
Lipophilic / Fat Soluble
Ionic aspirin

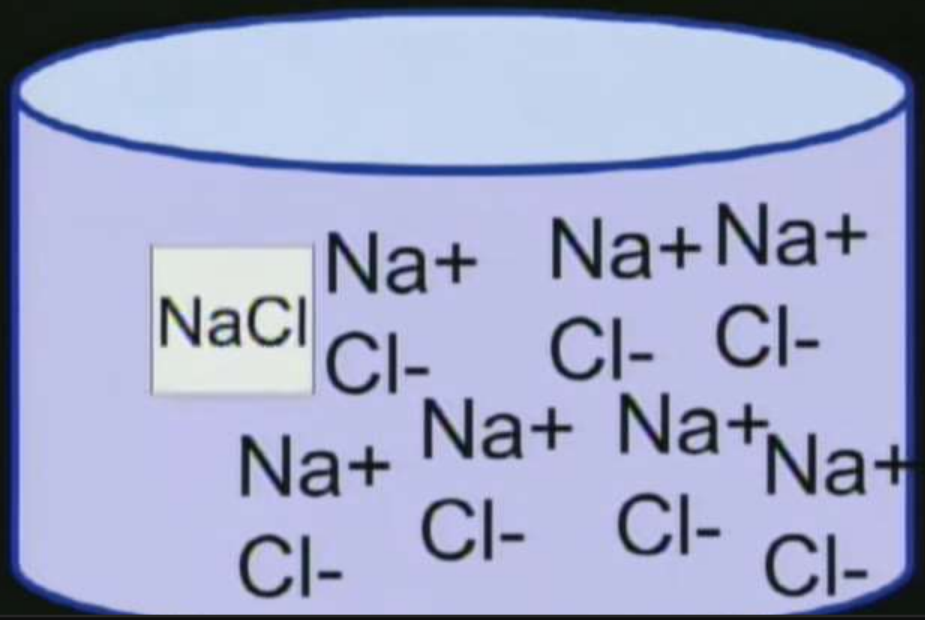
Aspirin


FOCUS


R - COOH
R-COO- H+
Uncharged aspirin
Lipophilic / Fat Soluble
Ionic aspirin
Hydrophilic / Water Soluble

Let’s go back to table salt, and talk about “mass action”.


FOCUS
NaCl
Na+
Cl-
Na+
Cl-


NaCl
Na+
Cl-
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Na+
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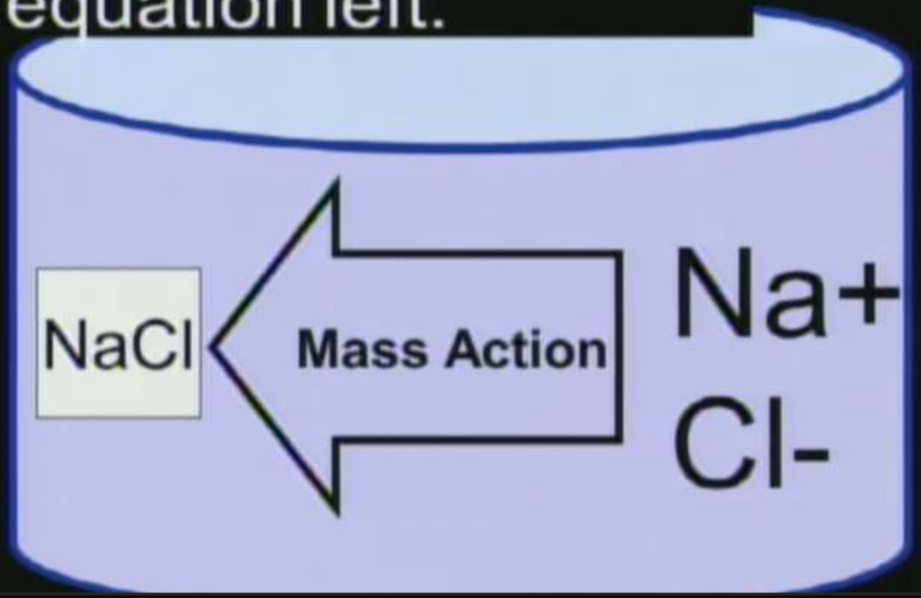
SATURATED

Instead of dissolving…
"Mass Action" pushes the equation left.



pH

- pH is a measure of acidity (< 7)
- pH is a measure of alkalinity (> 7)

Acidity pH < 7

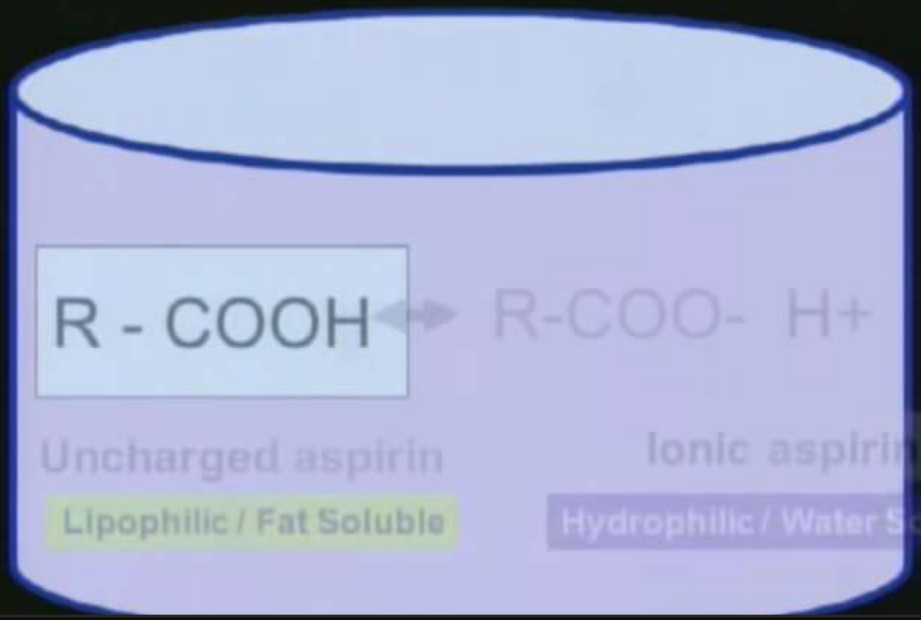
- Acidity means the solution has excess H+
- This “mass action” of H+ can push the equation toward the protonated form of the drug

Aspirin

R - COOH

Aspirin


FOCUS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Aspirin


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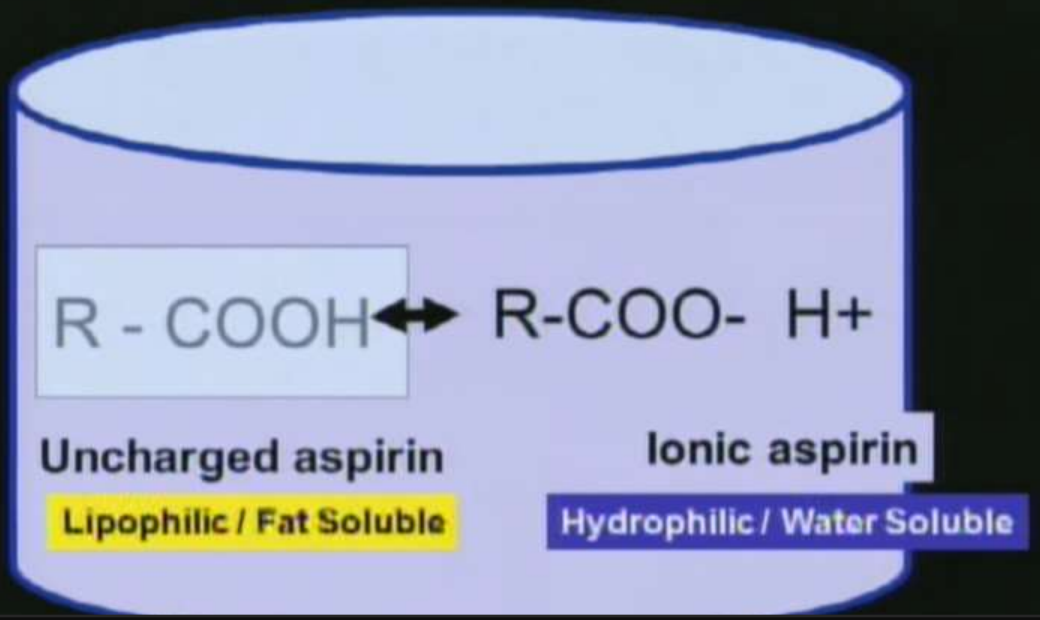
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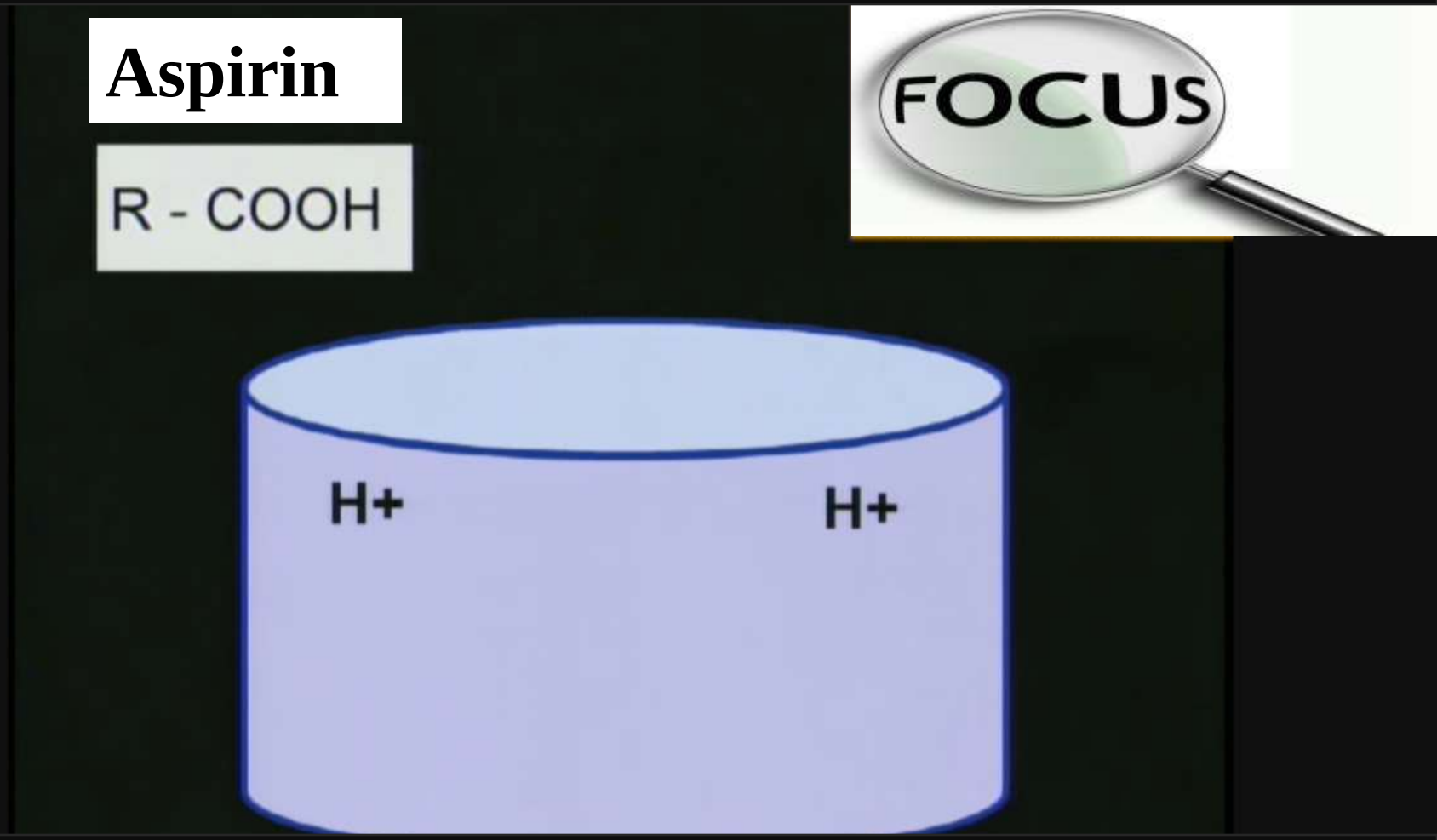
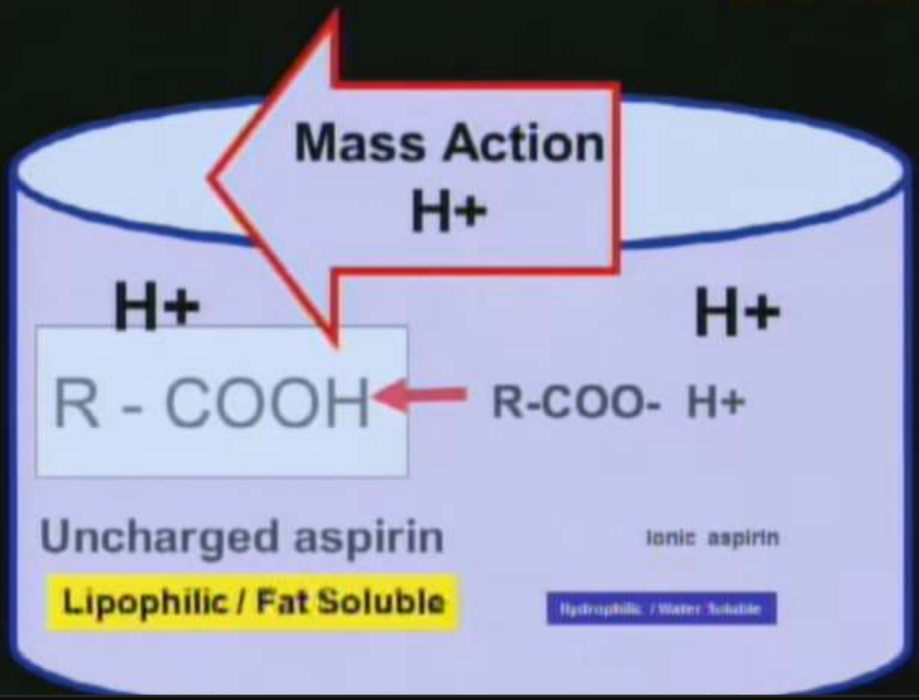


If the medium is acidic .i.e. Stomach

Aspirin



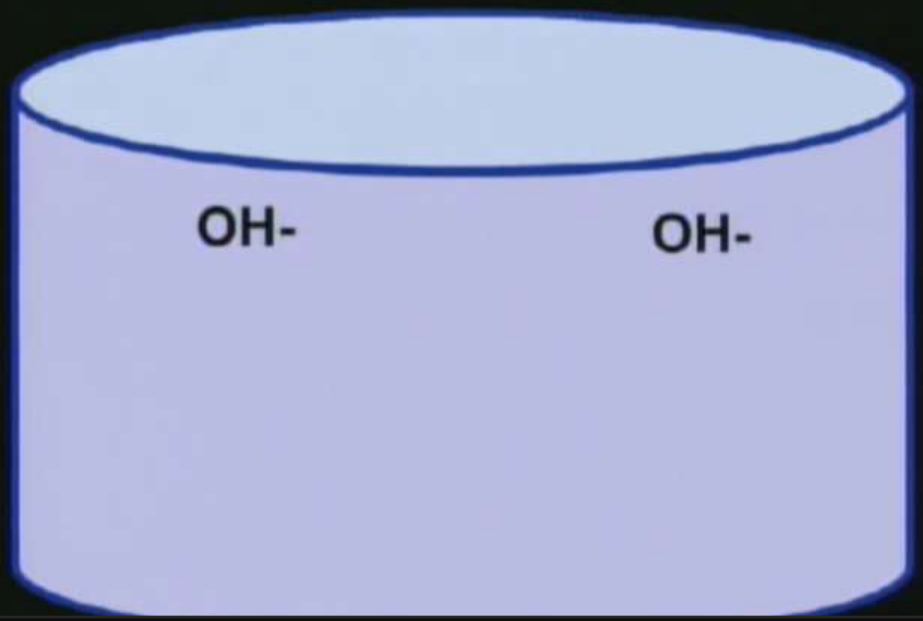
According to the low of mass action , most of aspirin will be in its protonated uncharged state which is more lipid soluble = better absorption .

Alkalinity pH > 7

- Alkalinity means the solution is able to remove any H+ from the solution
- This “mass action” of H+ can pull the equation toward the unprotonated form of the drug

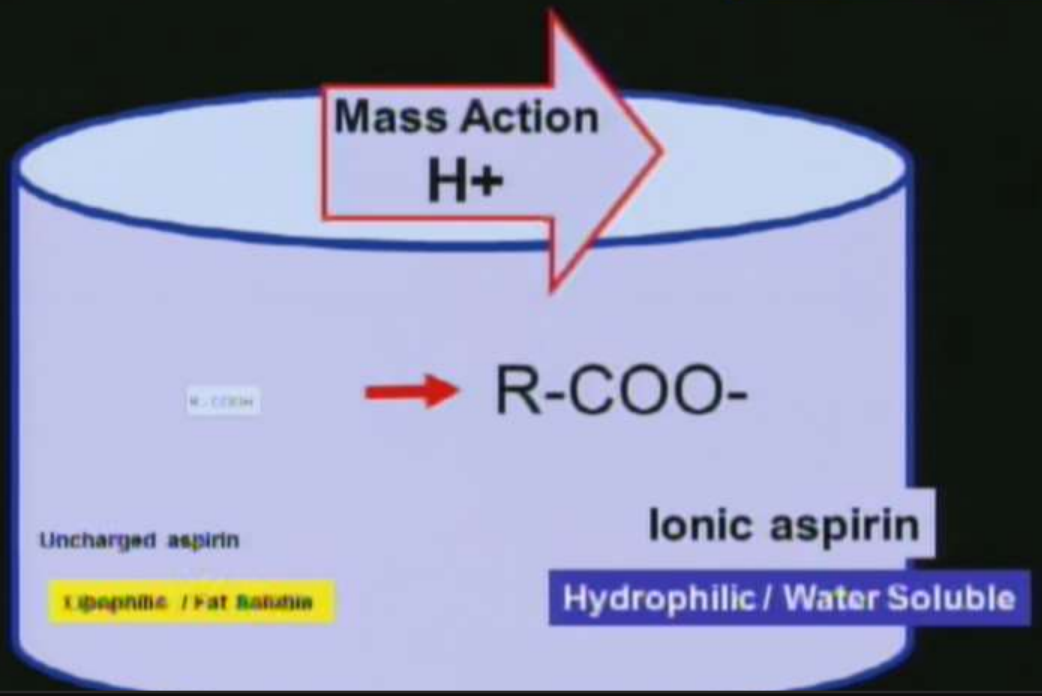
Aspirin

R - COOH



If the medium is alkaline .i.e. Small intestine

Aspirin



According to the low of mass action , most of aspirin will be in its unprotonated charged state which is less lipid soluble = less absorption .

2-Diffusion of drugs that are weak electrolytes

At a pH equals to the pK_a the drug is 50% ionised.

Thus, a weakly acidic drug (e.g. aspirin) in a medium of low pH (e.g. stomach) will be mainly in its undissociated form; → better absorption

2-Diffusion of drugs that are weak electrolytes

whereas a weakly basic drugs (e.g. amphetamines) in a medium of high pH (e.g. small intestine) will be mainly in its undissociated form. ; ⇒ better absorption

From 1&2

-Only the non ionized (uncharged) form of a drug crosses biomembranes .

(lipid soluble = better absorption)

- The ionized form is better renal excretion because it is water soluble.

(lipid insoluble = poor absorption but still better excretion)

TCA overdose

- In cases of Tricyclic Antidepressant overdose, we “alkalinize” the blood with sodium bicarbonate to change the drugs effect on the body.

2-Diffusion of drugs that are weak electrolytes

Ion trapping occurs when a drug that is a weak acid or weak base moves between fluid compartments with different pHs,

for example, when a drug given orally is absorbed from the stomach contents (with a pH of 1 to 2) to plasma with a pH of 7.4. The drug will tend to accumulate in the fluid compartment in which it is most highly ionized,
i.e.,
weak acids will tend to accumulate in the fluid with the higher ph and weak bases in the fluid with the lower ph
.

- Most drugs are weak acids or weak bases because only small changes in pH are required to shift between:
- **lipid soluble** (easily passes cell membranes)
- **water soluble** (does not pass without transport)

factors which influence absorption of drugs & Permeation :

- Solubility

Ability to diffuse through lipid bilayers (**lipid solubility**) is important for most drugs; however, **water solubility** can influence permeation through aqueous phases.

-Concentration gradient.

Diffusion down a concentration gradient

only free, unionized drug forms

contribute to the concentration gradient .

-Surface area and vascularity .

The larger the surface area and the greater the vascularity , the better is the absorption of the drug.

surface area and blood flow

The total surface area of the small intestine about 200 m^2, and an estimated perfusion 1 litre / minute.While the stomach are only 1 m^2 and 150 ml/min.

these increases in both surface area and blood flow more than compensate for the decreased fraction of unionised acid in the intestine.

In fact, the absorption of all compounds, acids, bases, or neutral compounds, is faster from the small intestine than from the stomach.

Sites of absorption

(1) Stomach

(a) Lipid-soluble drugs and weak acids, which are normally unionized at the low pH (1 to 2) of gastric contents, may be absorbed directly from the stomach.

(b) Weak bases and strong acids (pK = 2 to 3) are not normally absorbed from this site since they tend to exist as ionized (that carry either a positive or negative charge, respectively**).**

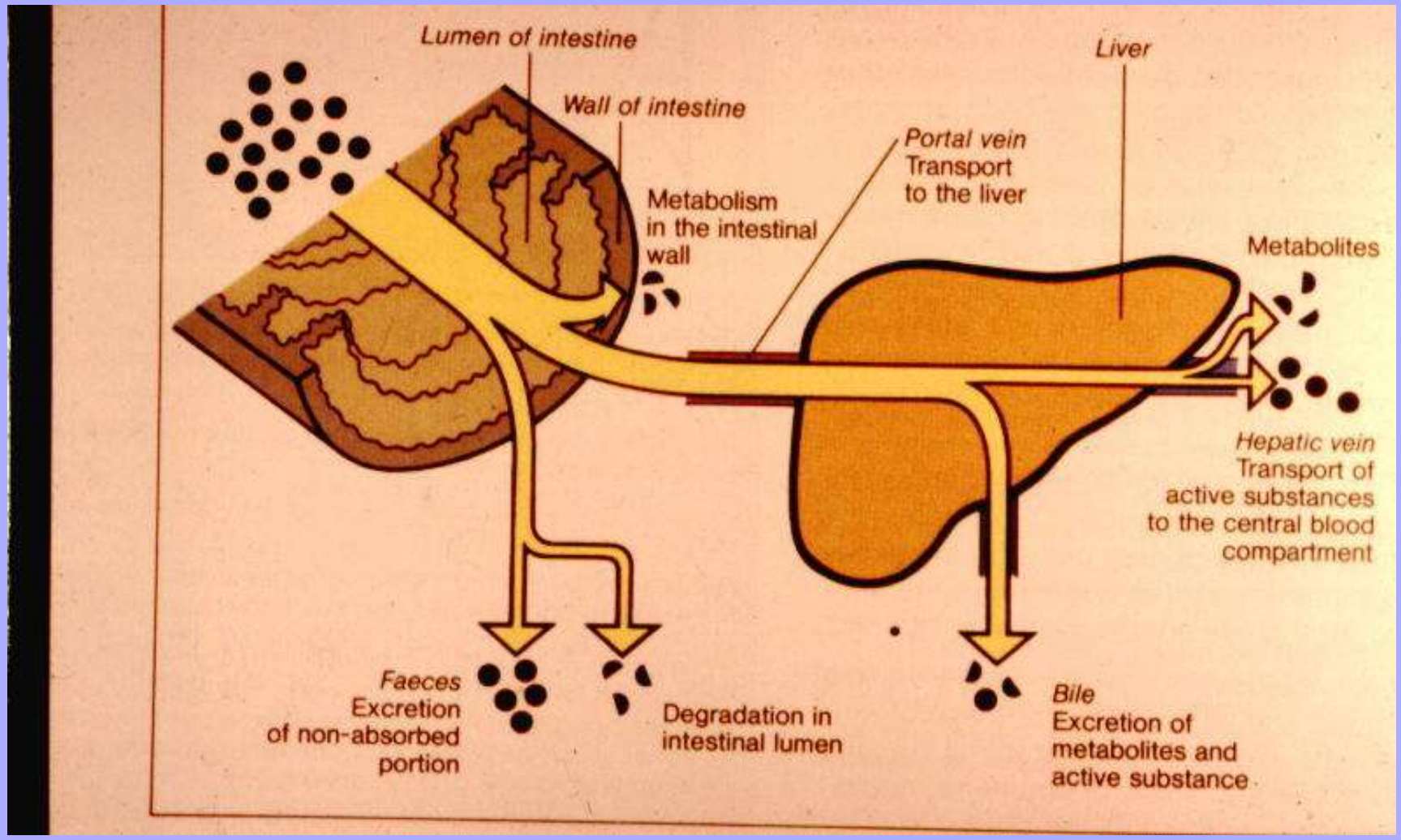
Sites of absorption

(2) Small intestine

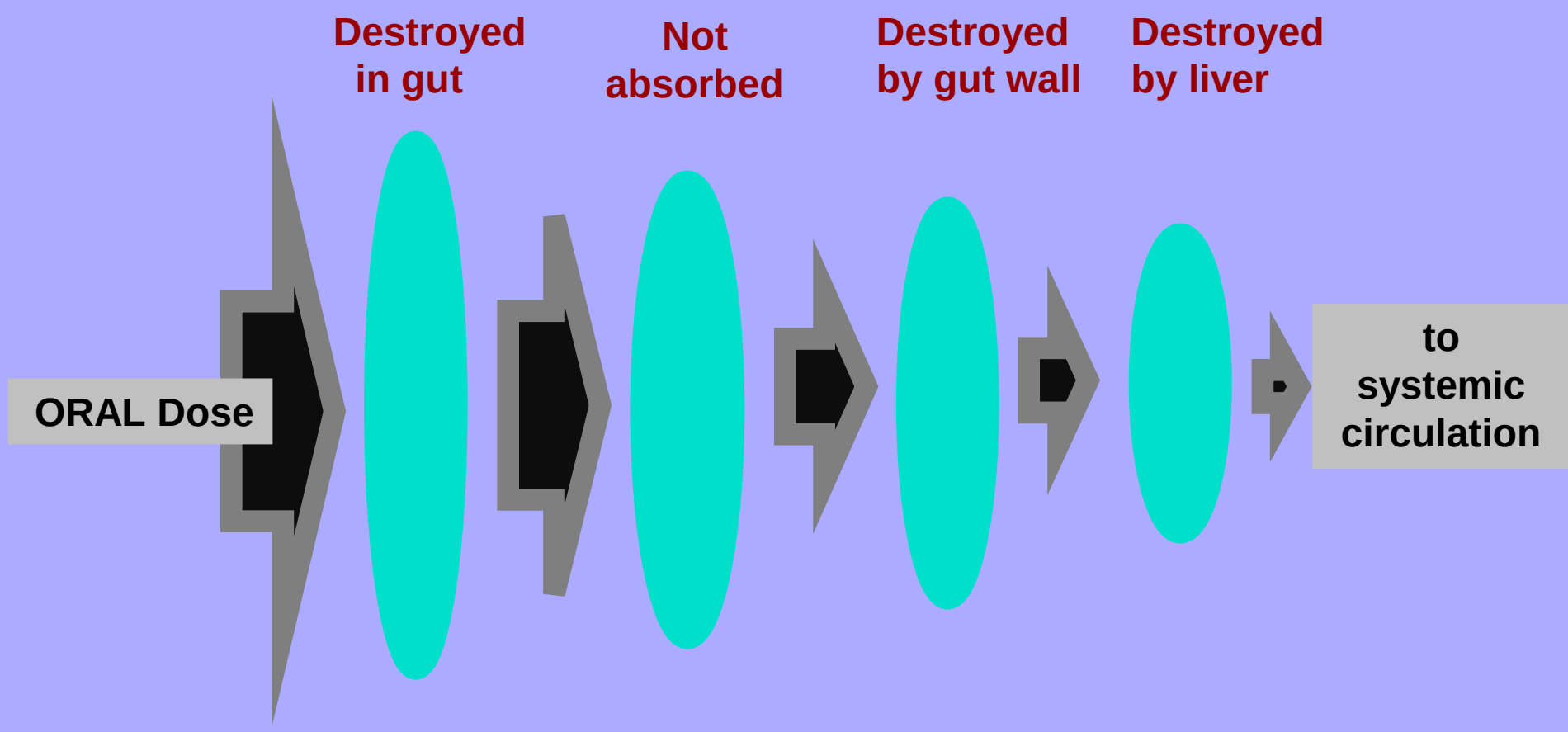
(a) The small intestine is the primary site of absorption of most drugs because of the very large surface area across which drugs, including partially ionized weak acids and bases, may diffuse.

(b) Acids are normally absorbed more extensively from the small intestine than from the stomach, even though the intestine has a higher pH i.e (approximately 5)

Bioavailability



Bioavailability

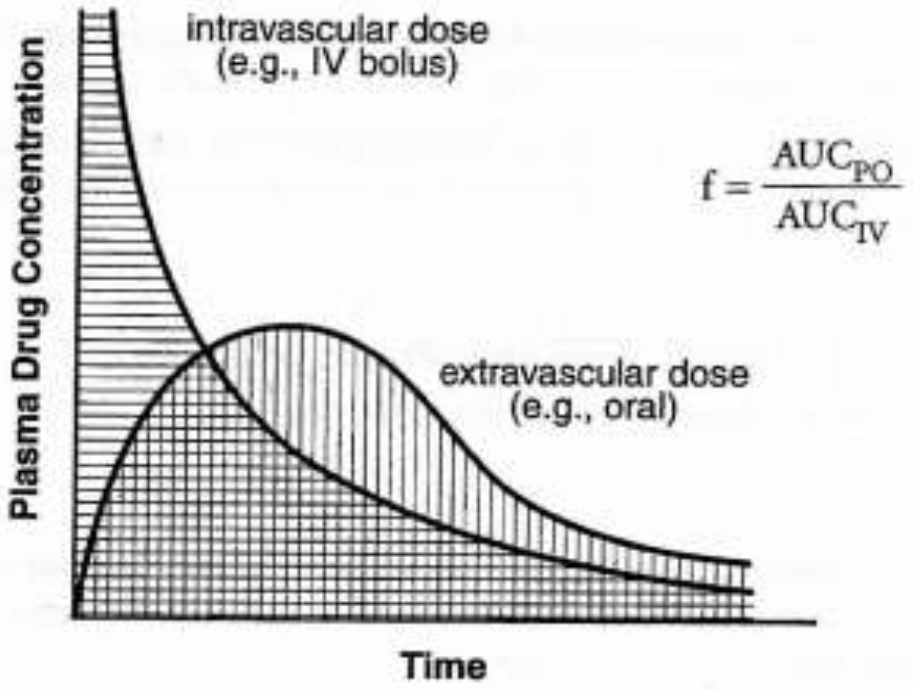


Bioavailability

- **Bioavailability of a drug is the ease (how much of the drug and how fast, completeness of absorption) at which it reaches the general circulation**

- **is the fraction of drug (administered by any route) that reaches the bloodstream unaltered**
(by hepatic metabolisim & or biliary excretion **)**
(bioavailability = 1 for intravenous administration)

Bioavailability



- Measure of the fraction of a dose that reaches the systemic circulation
- By definition, intravascular doses have 100% bioavailability , f = 1.

The first-pass effect

•influences drug absorption by metabolism in the liver or by biliary secretion.

• If the capacity of liver metabolic enzymes to inactivate the drug is great, only limited amounts of active drug will escape the process.

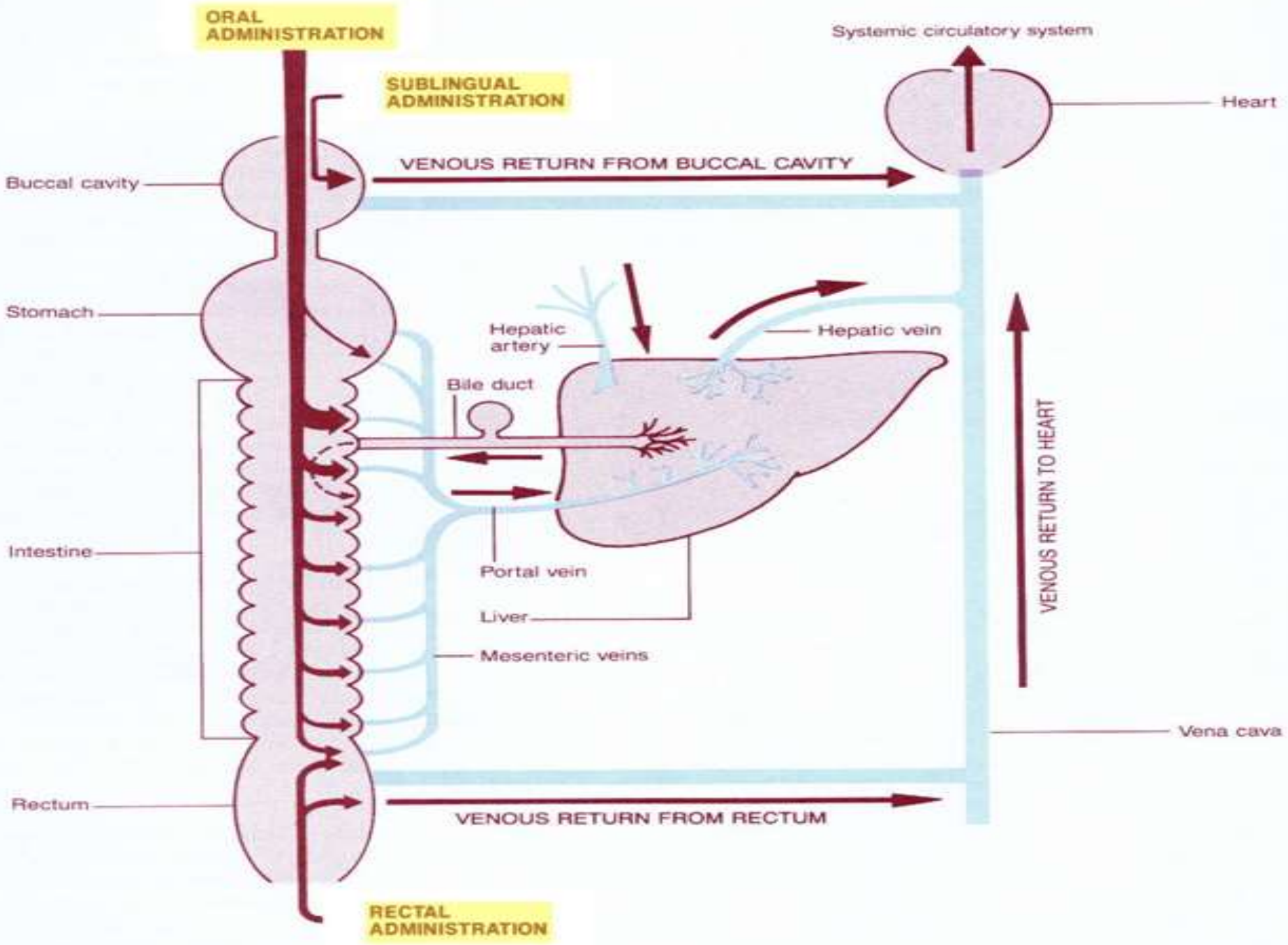
• Some drugs are metabolized so extensively as a result of hepatic metabolism during the first pass that it precludes their use.

Examples:

Nitroglycerin (sublingual)

Blood perfusing the buccal cavity bypasses the liver and enters directly into the superior vena cava.

Part of the rectal blood supply, particularly the inferior and middle haemorrhoidal veins, bypasses the hepatic portal circulation and dumps directly into the inferior vena cava.


ORAL ADMINISTRATION
SUBLINGUAL ADMINISTRATION
Systemic circulatory system
Heart
VENOUS RETURN FROM BUCCAL CAVITY
Buccal cavity
Stomach
Hepatic artery
Hepatic vein
Bile duct
Intestine
Portal vein
Liver
Mesenteric veins
VENOUS RETURN TO HEART
Vena cava
Rectum
VENOUS RETURN FROM RECTUM
RECTAL ADMINISTRATION

The rectal route has a definite advantage over the oral route for drugs that are destroyed by gastric acidity or by enzymes in the intestinal wall and microflora.

Plus avoiding the first pass effect (inferior rectal vein)

Enzymatic hydrolysis occurs to aspirin forming salicylic acid , active anti-inflammatory compound.

In fact, hepatic hydrolysis is so rapid that a significant fraction of aspirin is converted to salicylic acid in a single passage through the liver, resulting in a substantial “first-pass effect”.

Other factors that may alter absorption from the stomach or small intestine

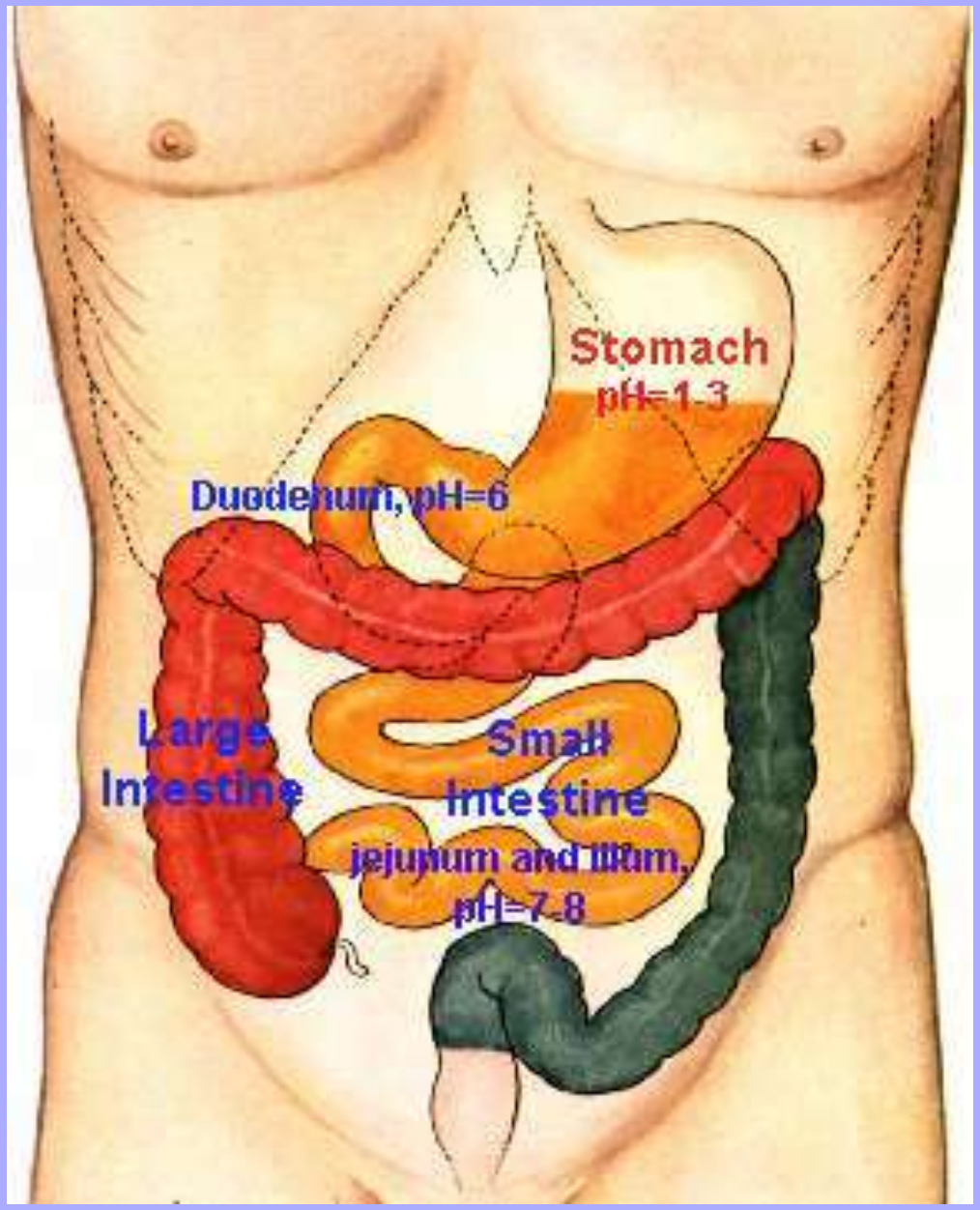
(a) Gastric emptying time and passage of drug to the intestine may be influenced by gastric contents and intestinal motility. A decreased emptying time generally decreases the rate of absorption because the intestine is the major absorptive site for most orally administered drugs.

(storage organ from which pulses of drug are ejected onto the absorptive sites in the small intestine.)

gastric emptying rate is a limiting step in the rapidity of drug absorption.

Consequently, food, particularly fat, slows stomach emptying.

This explains why drugs are frequently recommended to be taken on an empty stomach when a rapid onset of action is desired.



Griseofulvin

(and mebendazole and albendazole),

sparingly soluble

Fatty food slows gastric emptying

The Carrier system for absorbing riboflavin is located in the upper part of the small intestine.

At the does taken, the concentration of riboflavin reaching the site of absorption saturates the transport process.

The oral bioavailability of riboflavin can be increased by taking the vitamin with small amounts of food.

Other factors that may alter absorption from the stomach or small intestine

(b) Gastrointestinal (GI) blood flow plays an important role in drug absorption by continuously maintaining the concentration gradient across epithelial membranes.

The absorption of small, very lipid-soluble molecules is "blood flow limited," whereas highly polar molecules are "blood flow independent."

Blood flow and membrane permeability

At higher blood flow rates, however, membrane permeability becomes the rate–limiting step, and absorption is insensitive to blood flow

1. Low permeability properties
2. intermediate permeability properties
3. High permeability properties

Blood flow and membrane permeability

Some compounds, e.g. **urea**, have **intermediate permeability properties**. At **low blood flow rates**, the compound has sufficient time to diffuse across the membrane so absorption is **perfusion rate–limited**.

.

Other factors that may alter absorption from the stomach or small intestine

(c) Stomach acid and inactivating

enzymes may destroy certain drugs.

Benzyl penicillin when given orally

undergoes substantial hydrolysis by gastric acid;
therefore, it is administered by injection.

polypeptides : insulin is broken down by intestinal enzymes,

Enteric coating prevents breakdown of tablets by the acid pH of the stomach.

Other factors that may alter absorption from the stomach or small intestine

(d) Interactions with food, other drugs, and other constituents of the gastric milieu may influence absorption.

Tetracycline

undergoes complexation with polyvalent metal ions, e.g. Ca^{++}, Al^{+++}, forming **unabsorbed insoluble complexes.**

Other factors that may alter absorption from the stomach or small intestine

(e) Inert ingredients in oral preparations or the special formulation of those preparations may alter absorption.

For the same proprietary (trade) name,
a particular pharmaceutical preparation of a drug may exhibit

a widely different values of bioavailability

due to pharmacokinetic differences in the handling of the drug by the body including concurrent medications.
Ex .carbamezipine

2-Diffusion of drugs that are weak electrolytes

Streptomycin, a relatively water–soluble polar base, has difficulty penetrating the gastrointestinal mucosa (tight junction) ; it is rapidly absorbed from the intramuscular site.

Because

Diffusion through aqueous channels is not important because the channels are only 0.4nm wide and most drugs are at least 1nm in diameter.

Time for Absorption

If a drug is poorly permeable, polar compounds like **streptomycin**, **heparin**, **suxamethonium**, **and ipratropium**

there is insufficient time for complete absorption.

streptomycin, heparin, suxamethonium, and ipratropium

There absorption is controlled or rate limited by diffusion (penetration, permeability) through the membrane and not in removing the drug from other side of the membrane.

So they are sparely absorbed from GIT and usually given by other routes


Thank you