Inorganic Pharmaceutical Chemistry:

Gastrointestinal agents: Acidifying & Antacids agents

Assistant Lecturer: Hasanain Salah

3rd Year Pharmacy

Faculty of Pharmacy/ Al-Muthanna University

2023/2024

Introduction

❖Acidifying agents, antacids, and saline cathartics Agents used to treat gastrointestinal disturbance are known as ***gastrointestinal agents***. Various inorganic agents used to treat GIT orders include:

1. Products for altering gastric pH i.e. acidifying agents and antacids
2. Protectives and adsorbents
3. Saline cathartics or laxatives

Acidifying Agents

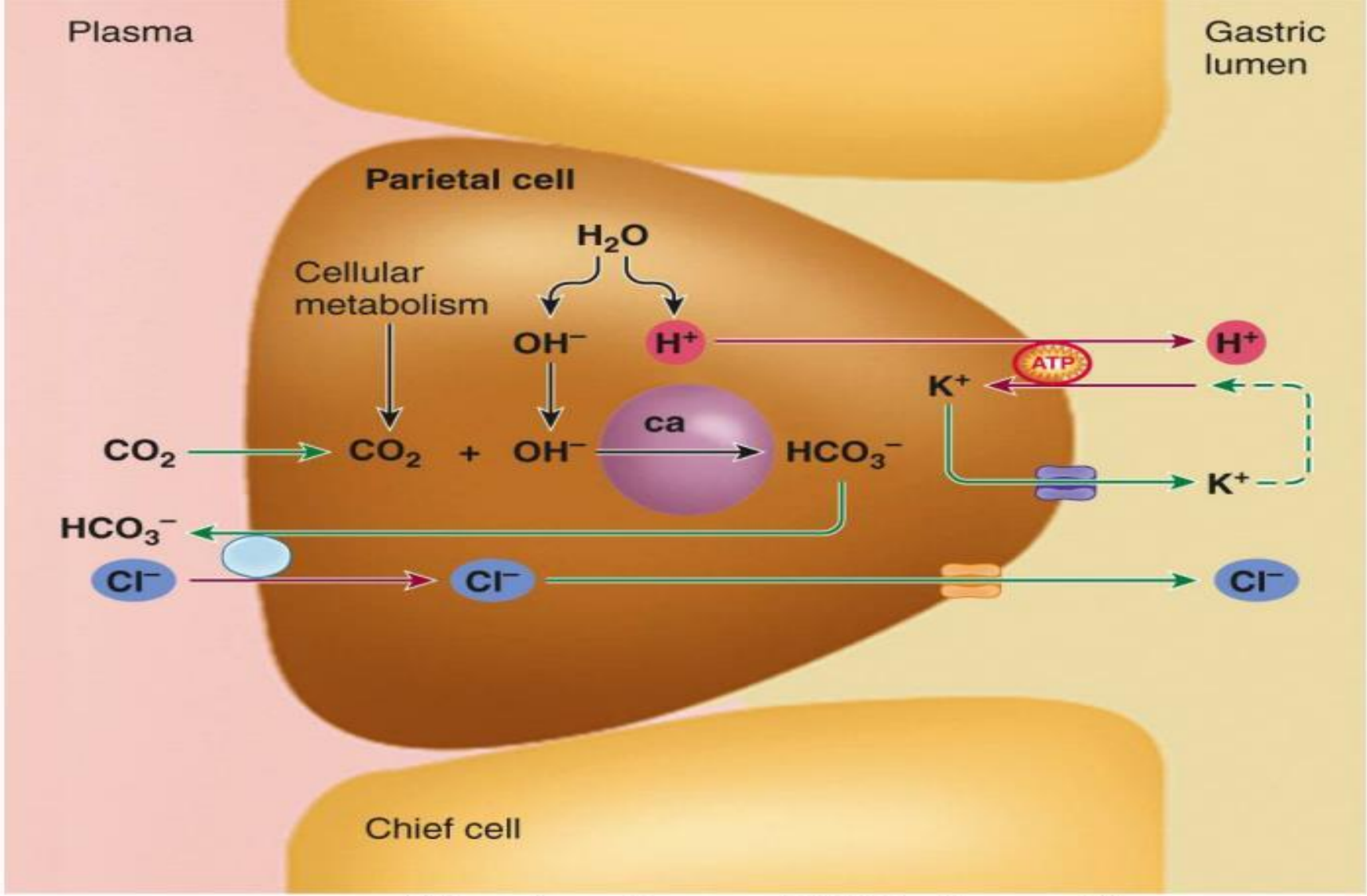
- The pH of the stomach is 1.5 -2 when empty and rises to pH 5-6 when food is ingested.
- The pH of the stomach is so low because of the secretion of HCl.
- Gastric HCl acts by destroying the bacteria in the ingested food and drinks.
- It softens the fibrous food and promotes the formation of the proteolytic enzyme pepsin. This enzyme is formed from pepsinogen at acidic pH (>6). Pepsin helps in the metabolism of proteins in the ingested food. Therefore lack of HCl in the stomach can cause Achlorhydria.
- Two types of achlorhydria are known:

1) where the gastric secretion is devoid of HCl, even after stimulation with histamine phosphate
2) where gastric secretion is devoid of HCl, but secreted upon stimulation with histamine phosphate.

- The cause of achlorhydria in the first case may be subtotal gastrectomy, atrophic gastritis, carcinoma, gastric polyp, etc while in later cases it may be chronic nephritis, tuberculosis, hyperthyroidism, chronic alcoholism, sprue, pellagra, etc.
- Achlorhydria occurs when there's an absence of hydrochloric (HCl) acids in the stomach. It's a more severe form of hypochlorhydria, a deficiency of stomach acids. Both conditions can impair the digestive process and lead to damage to the gastrointestinal system.
- The symptoms vary with an associated disease but they generally include mild diarrhea or frequent bowel movement, epigastric pain, and sensitivity to spicy food.
- Achlorhydria can be treated by various acidifying agents like ammonium chloride, dilute HCl, Calcium chloride, etc.

❑*Dilute Hydrochloric Acid (HCl; M.W 36.5)*

- The acid should be diluted with 25-50 volumes of water or juice and sipped through a glass tube to prevent reaction upon dental enamel.
- It is taken during or after meals and given in conjunction with iron therapy in hyperchromic anemia.
- **Preparation:** It is prepared by mixing 274gm of HCl and 726 gm of purified water.



Mechanism of HCL Secretion

KEY

= Active transport

= Secondary active transport

ca = Carbonic anhydrase

= Passive diffusion

= Chemical reaction

TUMS

ANTACIDS
& WHY THEY WORK

Antacids

- **Antacids** are substances that reduce gastric acidity resulting in an increase in the pH of the stomach and duodenum. Gastric acidity occurs due to excessive secretion of HCl in the stomach due to various reasons.
- The pH of the stomach is 1.5- 2.5 when empty and rises to 5-6 when food is ingested. Low pH is due to the presence of endogenous HCl, which is always present under physiological conditions.
- **When hyperacidity occurs the result can range from:**

1. gastritis (a general inflammation of gastric mucosa)
2. peptic ulcer or esophageal ulcer (lower end of esophagus)
3. gastric ulcer (stomach)
4. Duodenum ulcers

- Peptic ulcers occur due to defective esophageal sphincter as in hiatal hernia. Gastric ulcers occur in lesser curvature and are found in first portion of the duodenum.
- Symptoms include uncomfortable feeling from overeating, heartburn, and growing hungry between meals.
- Complications involved are hemorrhage (being more common with duodenal ulcers), and perforation. Depending upon the severity and location of an ulcer treatment will range from diet and antacids and /or anticholinergic therapy to complete bed rest to surgery.
- Small meals after short interval help in reducing acidity, stimulants of gastric acid must be avoided like coffee, alcohol, spicy food, oil or fried food.
- These are the agents that decrease gastric acidity by neutralizing HCl.
- Many used in the condition called hyperchlorhydria give relief of pain due to Hyperchlorhydria (HCH).
- The effectiveness of antacids is measured in neutralizing capacity.
- In normal HCl is secreted by parietal cells of gastric mucosa depending upon the intake of food.
- Due to inflammation of gastric mucosa as in gastritis, there results in hypersecretion-of HCL called H.C.H.

- **Treatment:-** Anticholinergic drugs, use of certain type of food, antacids

I. As antacids are alkaline in bases they neutralize the acidity occurred in H.C.H.

II. Production is continuous therefore the use of antacids is required but antacids should act gradually without producing rebound acidity.

III. As antacids are used for longer periods they may produce side effects.

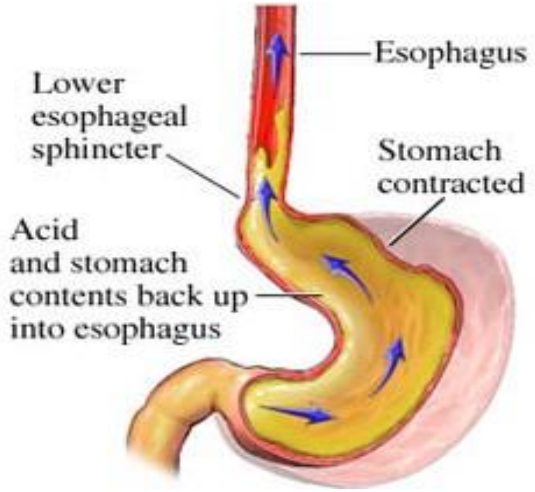
IV. To produce good effects with fewer side effects; **should have the following properties:**

✓**Ideal Characteristics of Antacid**

1) It should not be absorbable and cause systemic alkalosis
2) It should not be laxative or cause constipation
3) It should exert effect rapidly & over a long period of time
4) It should buffer in pH 4-6.
5) It should not produce a large volume of gas
6) It should be palatable & inexpensive
7) It should probably inhibit pepsin

❑ *Antacids are of two types:*

1. Systemic(absorbable) antacids: which are soluble readily absorbable and capable of producing systemic electrolytic alterations & alkalosis. E.g. sodium bicarbonate.
2. Non-systemic (non-absorbable) antacids:- which a not absorbed to a significant extent and thus do not exert an appreciable systemic effect.



This group is further subdivided into the following:

A. Aluminum-containing antacids:- Are non-systemic, and they tend to be constipating, because of the liberation of an astringent aluminium cation. Most cause increased faecal phosphate excretion due to the formation of insoluble aluminium phosphate in the intestinal tract.

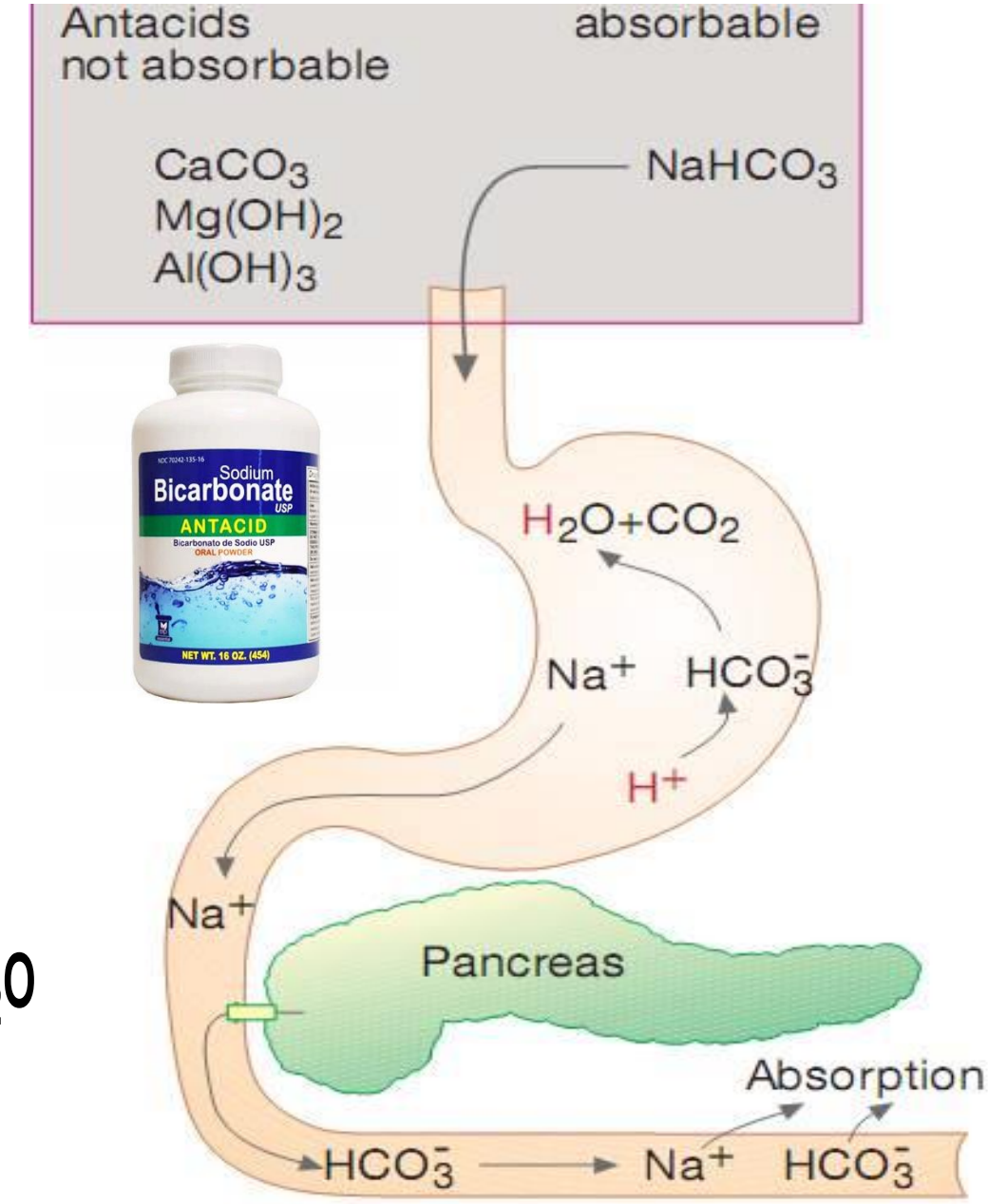
B. **Calcium-containing antacids:-** Eg. Calcium Carbonate tribasic calcium phosphate

C. **Magnesium containing antacids:-**Eg. magnesium carbonate magnesium citrate, magnesium hydroxide, magnesium oxide magnesium phosphate, magnesium trisilicate

D. **Combination antacid preparations:-** e g Aluminum Hydroxide gel & Magnesium Hydroxide, Aluminum Hydroxide gel, Magnesium trisilicate, Magaldrate Simethicone (deforming agent) containing Antacids, Calcium carbonate containing antacid mixtures

Sodium Bicarbonate

- Sodium bicarbonate **$NaHCO_3$** (backing soda)
- It is a highly water-soluble antacid.
- Has a very rapid onset and a short duration of action.
- Sodium bicarbonate can cause flatulence, because of the evolution of carbon dioxide in the presence of acid.
- Inhibit the absorption of tetracycline from GIT.
- Tetracyclines form insoluble complex molecules by metal ion chelation with various antacids; tetracycline absorption may be decreased by more than 90% by this interaction.

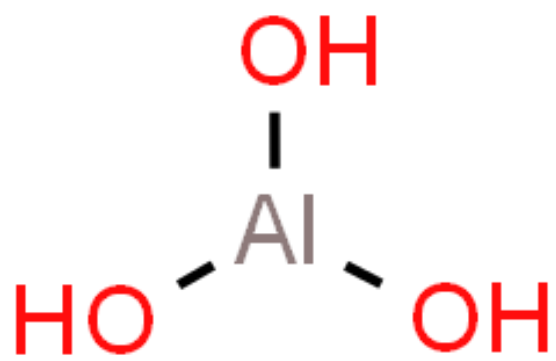


$$NaHCO_3 + HCl \longrightarrow NaCl + CO_2\uparrow + H_2O$$

Aluminum Hydroxide

- Aluminum Hydroxide : as Aluminum hydroxide gel and Dried Aluminum hydroxide
- Both the gel and dried gel have a slower onset of action.
- This varies with the dosage form and age of the product.
- The gel with its more finely divided particle and its ability to be completely wetted has a more rapid onset of action than the various dried gel tablets.
- The onset of action of the dried gel tablets will vary, depending on whether the patient must first chew the tablet or simply suck on the tablet. If chewing is required, then the degree of chewing will determine how finely divided will be the particles.
- Both the gel and dried gel have a problem of a loss of antacid properties on aging.
- The rate of loss of antacid action depends upon the pH used to precipitate the gel.
- Aluminum hydroxide gels are ideal buffers in the pH3-5 region due to their amphoteric character.

Base		Acid		Conjugate Acid		Conjugate Acid	
$[Al(H_2O)_3(OH)_3]$	+	H_3O^+	⇌	$[Al(H_2O)_4(OH)_2]^+$	+	H_2O	1
$[Al(H_2O)_4(OH)_2]^+$	+	H_3O^+	⇌	$[Al(H_2O)_5(OH)]^{+2}$	+	H_2O	2
$[Al(H_2O)_5(OH)]^{+2}$	+	H_3O^+	⇌	$[Al(H_2O)_6]^{+3}$	+	H_2O	3



Aluminum Phosphate Gel

- Aluminum phosphate gel (AlPO4), Phosphagel :-
- It is a non-absorbable antacid and exerts a little systemic effect.
- It has been used in place of aluminum hydroxide gel where loss of phosphate may be a problem for the patient. Since aluminum phosphate gel is regenerated in the intestine, endogenous phosphate is spared.
- It has adsorptive and astringent properties that are much the same as those of aluminum hydroxide gel.
- The acid-consuming ability of aluminum phosphate is based on the release of phosphate anion:-

$$AlPO_4 \rightleftharpoons Al^{+3} + PO_4^{-3}$$

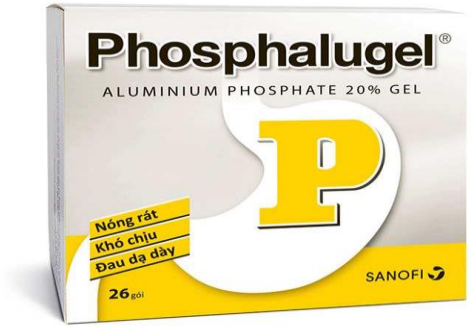
Solid — Solution

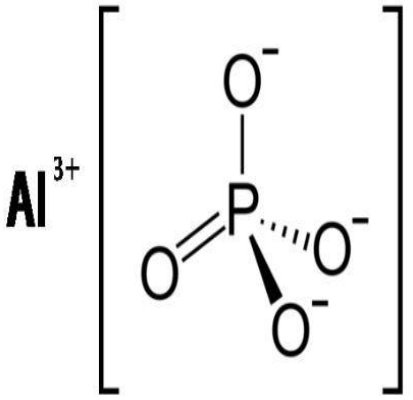
$$PO_4^{-3} + H_3O^+ \longrightarrow HPO_4^{-2} + H_2O$$

Base — Acid — Conjugate Acid — Conjugate Base

$$HPO_4^{-2} + H_3O^+ \longrightarrow H_2PO_4^{-1} + H_2O$$

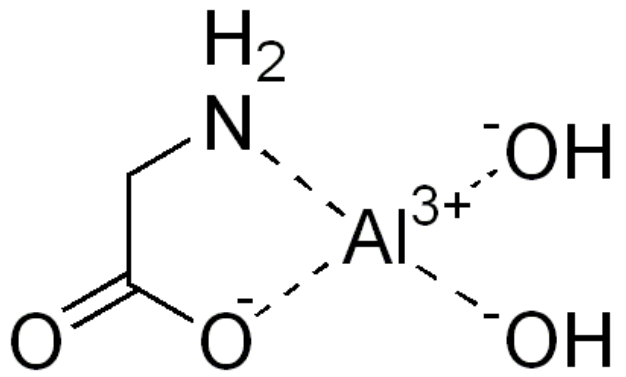
Base — Acid — Conjugate Acid — Conjugate Base





Di Hydroxy Aluminum Amino Acetate

- Di hydroxy aluminum amino acetate (**$NH_2CH_2COO\text{-}Al(OH)_2.xH_2O$**)
- This is non-absorbable and exerts little systemic effect.



- This product acts more promptly than the aluminum hydroxide gels because the amine group of glycine reacts with the gastric acid forming the protonated amine.

$$NH_2CH_2CO_2Al(OH)_2 + H_3O^+ \longrightarrow NH_3^+CH_2CO_2Al(OH)_2 + H_2O$$

- This is followed by a reaction with the two hydroxyls and the glycine carboxyl group resulting in a prolonged buffering action:-

$$NH_3^+CH_2CO_2Al(OH)_2 + H_3O^+ \longrightarrow Al^{3+} + NH_3^+CH_2COOH + 2H_2O$$

Di Hydroxyl Aluminium Sodium Carbonate

- Di hydroxyl aluminium sodium carbonate[$(HO)_2AlOCO_2Na.xH_2O$]
- It is a non-absorbable aluminum antacid that has a rapid onset of action (REACTION 1).
- followed by a more prolonged reaction and a buffering action (REACTION 2, 3 and 4)

????

$$NaOCO_2Al(OH)_2 + H_3O^+ \longrightarrow Al(OH)_3 + Na^+ + CO_2\uparrow + H_2O \quad \text{---------- (1)}$$

$$[Al(H_2O)_3(OH)_3] + H_3O^+ \longrightarrow [Al(H_2O)_4(OH)_2]^+ + H_2O \quad \text{---------- (2)}$$

$$[Al(H_2O)_4(OH)_2]^+ + H_3O^+ \longrightarrow [Al(H_2O)_5(OH)]^{+2} + H_2O \quad \text{---------- (3)}$$

$$[Al(H_2O)_5(OH)]^{+2} + H_3O^+ \longrightarrow [Al(H_2O)_6]^{+3} + H_2O \quad \text{---------- (4)}$$

- Aging has little effect on efficacy.
- Potential drawbacks to this preparation would be the presence of sodium and evolution of carbon dioxide, and the usual problem associated with the aluminum antacids.

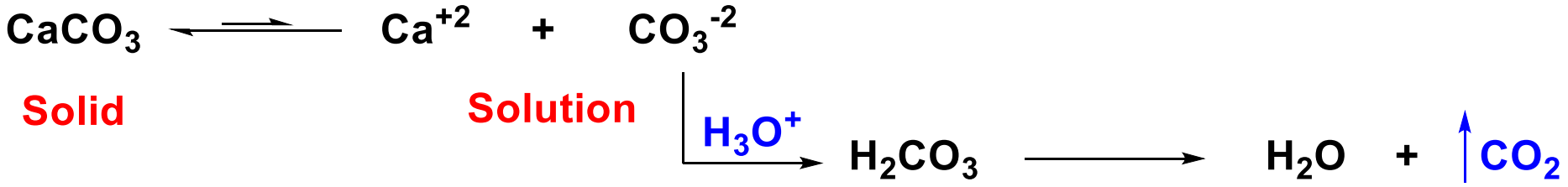
Calcium-Containing Antacid

1. The calcium-containing antacids differ from the aluminum antacids in that their action is dependent upon their basic properties and not on any amphoteric effect.
2. The calcium–containing antacids are rapid-acting and largely non-systemic.
3. They do not cause systemic alkalosis.
4. The liberated calcium cation can be absorbed; causing increased serum calcium levels, and renal failure due to hypercalcemia has been reported.
5. They cause an uncommon but potentially very serious side effect is the milk-alkali syndrome (Burnett syndrome). This can occur during prolonged administration of large doses of calcium carbonate together with large amounts of milk.
6. The calcium antacids tend to be constipating and are usually found in combination with magnesium antacids.

- **Alkalosis** is an abnormal pathophysiological condition characterized by the buildup of excess base or alkali in the body. It results in an abnormally high serum pH (arterial pH greater than 7.45), which is termed alkalemia, and forms one end of the spectrum of acid-base disorders.

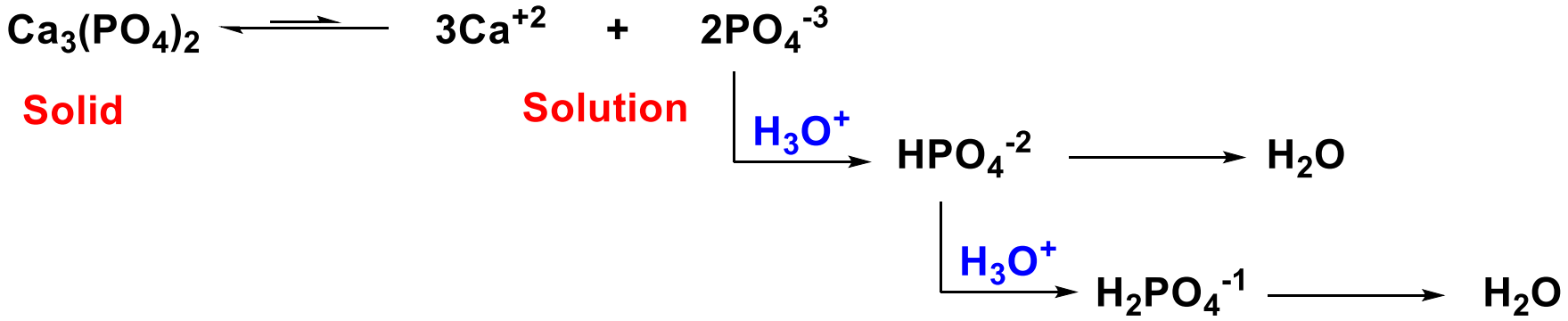
❑ *Calcium Carbonate $CaCO_3$*

- Its action is limited by the amount of salt that will go into the solution. Thus as gastric hydrochloric acid consumes the solubilized calcium carbonate, more goes into solution. This process continues until the acid or calcium carbonate is consumed.

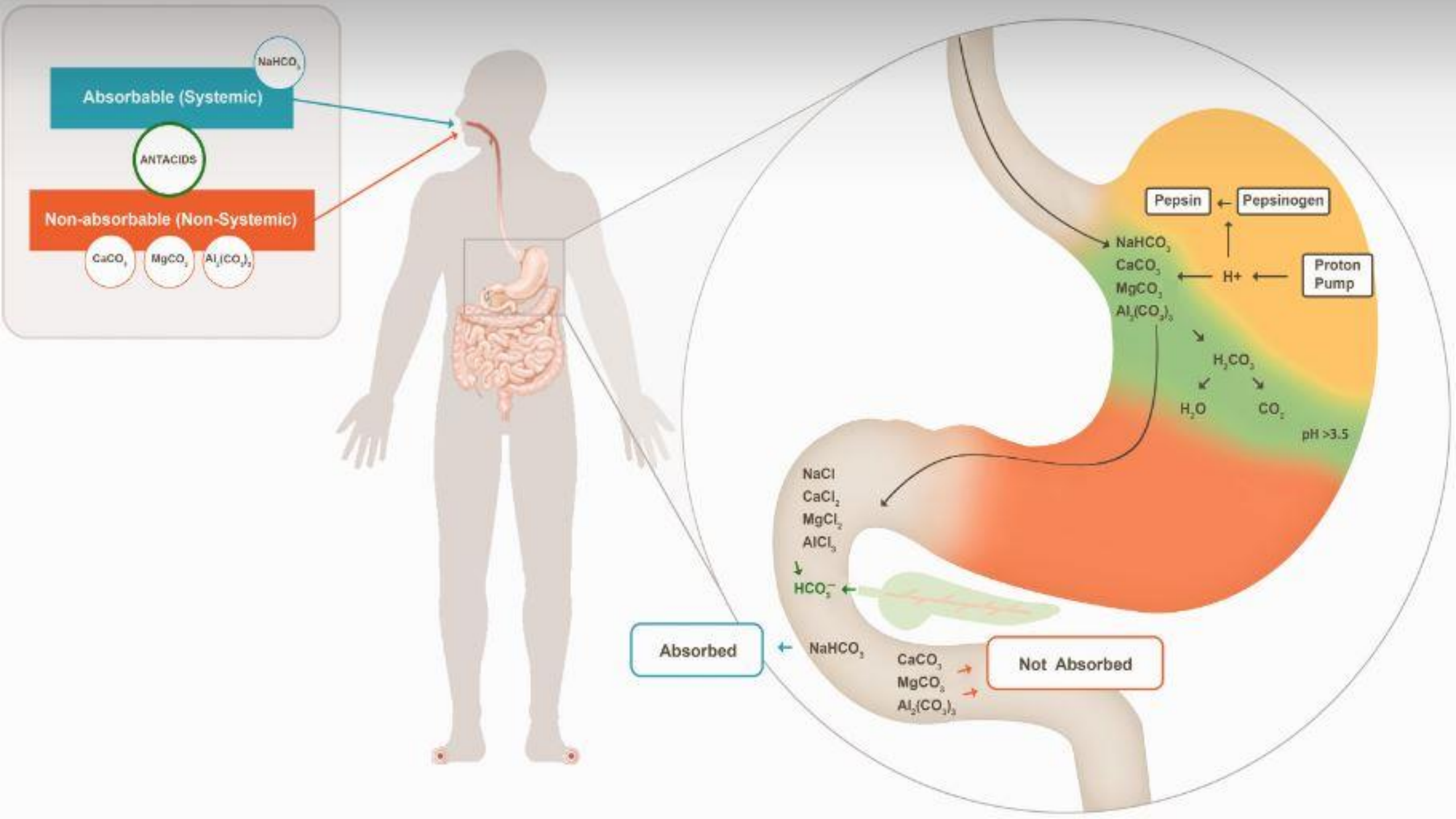


❑ *Tribasic Calcium Phosphate $[Ca_3(PO_4)_2]$*

- The principle of its action is based on its going into solution only in acid media, much the same as calcium carbonate. The phosphate anion then consumes two equivalents of gastric acid:-



- **Mainly used as a calcium replenisher.**


Absorbable (Systemic)
NaHCO3
ANTACIDS
Non-absorbable (Non-Systemic)
CaCO3
MgCO3
Al2(CO3)3
Pepsin
Pepsinogen
NaHCO3
CaCO3
MgCO3
Al2(CO3)3
H+
Proton Pump
H2CO3
H2O
CO2
pH >3.5
NaCl
CaCl2
MgCl2
AlCl3
HCO3−
Absorbed
NaHCO3
CaCO3
MgCO3
Al2(CO3)3
Not Absorbed

Magnesium-Containing Antacid

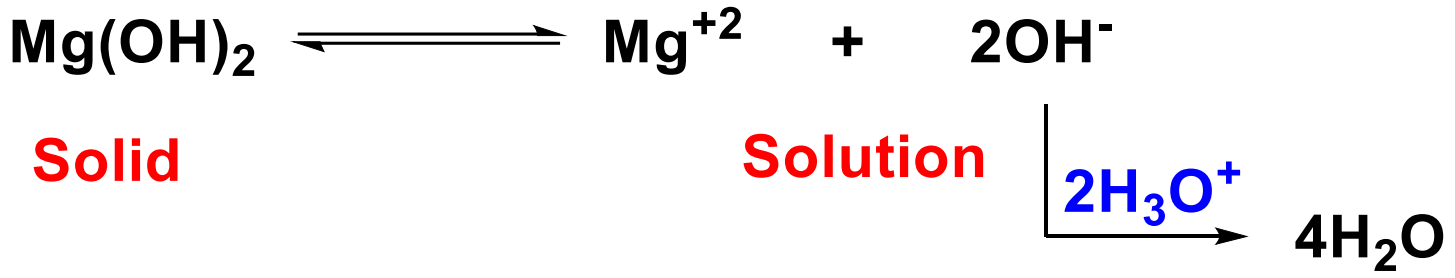
- They are poorly soluble salts that only go into solution as acid consumes the small amount of anion already in solution.
- As the pH of the stomach approaches neutrality, the rate of dissolution of the magnesium salts lowers and stops at neutrality. Thus, it is the anion rather than the magnesium cation that confers the antacid properties.
- The magnesium cation causes this group of antacids to be laxatives. For this reason, they are usually found in combination with aluminium and calcium antacids in an attempt to equalize constipation and laxative actions.

❑*Magnesium Carbonate*

- Approximate formula $(MgCO_3)_4$-$Mg(OH)_2.5H_2O$
- Is a hydrated mixture of magnesium carbonate MgCO3 and magnesium hydroxide.
- The antacid properties of magnesium carbonate are due to the carbonate and hydroxide anions reacting with the gastric hydrochloric acid. Due to its very limited solubility, magnesium carbonate dissolved only as carbonate and hydroxide are being consumed.

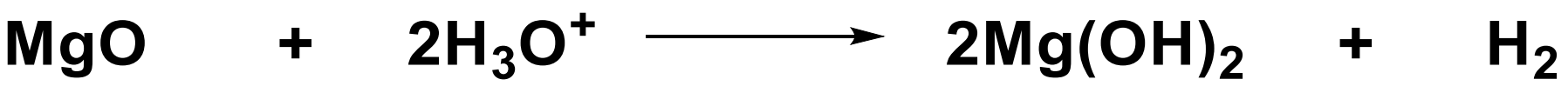
❑*Magnesium Hydroxide [$Mg(OH)_2$]*

- Magnesium hydroxide goes into solution as the anion (hydroxide) is consumed by the gastric hydrochloric acid.



❑*Magnesium Oxide (MgO)*

- In the presence of acid, the oxide is converted to the hydroxide and therefore, the chemistry and pharmacology are the same as those of magnesium hydroxide.



Combination Antacid

- Because no single antacid meets all the criteria for an ideal antacid, several products are on the market containing mixtures of antacids.
- Most of these combination products are

1. An attempt to balance the constipation effect of calcium and aluminum with the laxative effect of magnesium.
2. Some of these products are also a mixture of an antacid with a rapid onset of action and one with a supposedly longer duration of action.