PHARMACEUTICAL INORGANIC CHEMISTRY: Gastrointestinal agents (ANTACID)

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❖ Drugs Acting on the Gastrointestinal System

- The **Gastrointestinal** (GI) **Tract** includes the mouth, stomach, small intestine (duodenum, jejunum, and ileum), large intestine (cecum and colon), rectum, anus, and its accompanying exocrine glands (the salivary glands, the pancreas, and the gallbladder).
- Drugs affecting the GI system are used in the treatment of **Gastric Acidity**, **Peptic Ulcers**, and **Gastro Esophageal Reflux Disease** (GERD), **Bowel Motility Disorders** (*gastroparesis* [delayed gastric emptying due to partial paralysis of the stomach muscles], *constipation*, and *diarrhea*), and for the treatment of nausea and vomiting.

• Gastric acid production

- Gastric acid is secreted from parietal cells when stimulated by the vagus nerve, histamine, and gastrin. CO_2 and H_2O react inside parietal cells, under the influence of carbonic anhydrase, to form bicarbonate (**HCO_3^-**) and **H^+**.
- **H^+** is then pumped into the lumen of the stomach by **H^+/K^+ ATPase**.
- **Cl^-** is also secreted from parietal cells into the lumen by simple diffusion.
- Then this **H^+, Cl^-** and **water** combine in the lumen to form hydrochloric acid (**HCl**).
- The **HCO_3^-** produced is secreted into the bloodstream.

➢ Gastric Antacids

- **Antacids** (*anti* - against; acidus - acid) are weak alkaline compounds used to neutralize hydrochloric acid in the stomach.
- Antacids are the substances which reduce gastric acidity resulting in an increase in the pH of stomach and duodenum. Gastric acidity occurs due to excessive secretion of HCl in stomach due to various reasons.
- The pH of the stomach is **1.5- 2.5** when empty and raises 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:
    i. Gastritis (a general inflammation of gastric mucosa)
    ii. Peptic ulcer or oesophageal ulcer (lower end of oesophagus)
    iii. Gastric ulcer (stomach)
    iv. Duodenum ulcers
- ***Symptom of hyperacidity:***
    - Hydrochloric acid is secreted by the stomach to kill harmful organisms, aid digestion and activate digestive enzymes.
    - Excess secretion of acid into stomach or impaired resistance by the lining of the stomach or reflux into the oesophagus may produce symptoms.
    - Hyperacidity cause gastric reflux, gastritis, upset stomach and heartburn.
- ***Criteria of an ideal antacid preparation:***
    - The antacid should not be absorbable or cause systemic alkalosis
    - The antacid should not be a laxative or causes constipation
    - The antacid should exert its effect rapidly and over a long period of time
    - The antacid should buffer in the pH **4-6** range
    - The reaction of the antacid with gastric HCl acid should not cause a large evolution of gas
    - The antacid should probably inhibit pepsin

- ***Classification of antacids***
  - Antacids can be classified into two main category:

i. Based on chemical nature of Antacid properties.

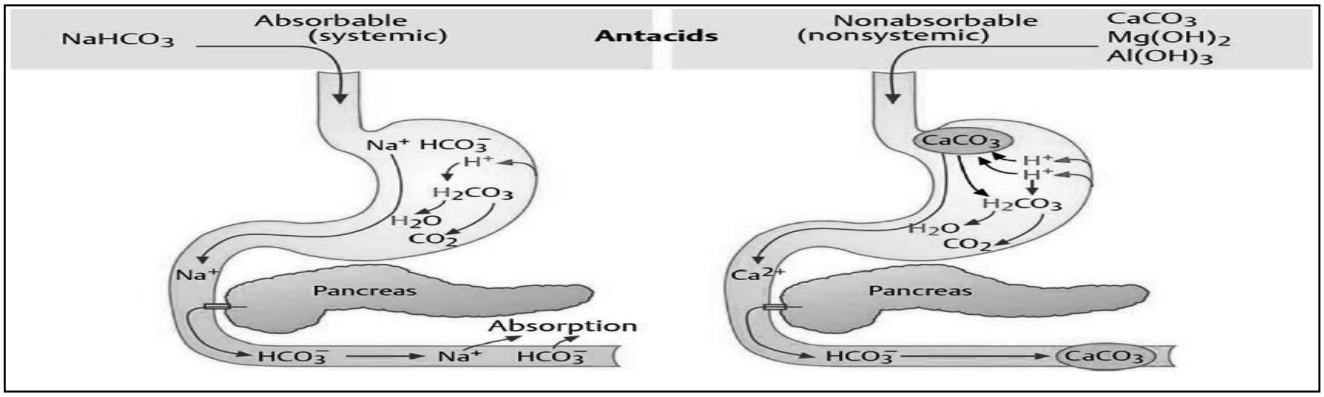
Absorbable Antacids	**Non-Absorbable Antacids**
o The absorbable antacids (chemical antacids) show the most rapid onset of action and provide faster relief of symptoms. o However they may cause an "acid rebound". o Absorbable Antacids inappropriate for patients afflicted with hypertension or kidney failure.	o The non-absorbable antacids though less prone to cause a rebound effect o Moreover as these antacids are more potent and effective in a semi liquid or liquid form than in a capsule or table o The usually high presence of aluminum and magnesium hydroxides in non-absorbable antacids can be effectively used to prevent significant stress ulcer bleeding in post-operative patients or those with severe burns.
Example	*Example*
▪ Sodium bicarbonate (baking soda) ▪ Magnesium oxide (magnesia) ▪ Magnesium carbonates ▪ Calcium carbonates ▪ Bourget mixture (sodium bicarbonates, sulphate, phosphate) ▪ Rennie mixture (calcium carbonates, magnesium carbonates); ▪ Tums mixture (calcium carbonates, magnesium oxide).	▪ Aluminum Phosphate ▪ Aluminum Hydroxide ▪ Magnesium Silicate ▪ Magnesium Hydroxide ▪ Aluminum-Magnesium Combination

ii. Based on pharmacological properties of Antacid.

Non-systemic antacids	**Systemic antacids**
o Non-systemic antacids are compounds that are not absorbed into the systemic circulation. o Their anionic group neutralizes the H^+ ions in gastric acid. This releases their cationic group which combines with $\mathbf{HCO_3^-}$ from the pancreas to form an insoluble basic compound that is excreted in feces. o Thus these agents do not produce metabolic alkalosis.	o Systemic antacids are absorbed into the systemic circulation. o They have a cationic group that does not form insoluble basic compounds with $\mathbf{HCO_3^-}$. o Thus the $\mathbf{HCO_3^-}$ can be absorbed producing a metabolic alkalosis.
Example	*Example*
▪ Aluminum Hydroxide ▪ Magnesium Hydroxide	▪ Sodium bicarbonate

Non-absorbable antacids have many others favorable properties
▪ Absorb pepsin, resulting in reduced proteolytic activity of gastric acid.
▪ Connect lysolecithin and bile acid, which have a damaging effect on the gastric mucosa.
▪ Possess cytoprotective function through the activation of prostaglandin synthesis, which stimulate a secretion of mucin and bicarbonates, improve microcirculation.
▪ Possess ambient function, forming a protective film on the gastric mucosal surface.
▪ Able to bind epithelial growth factor and fix it in the ulcerous defect region effectively stimulating cell proliferation, angenesis and angiogenesis.

- ***Mechanism of antacid:***
  - Antacids were developed based on the hydroxides and carbonates of the group II and III metals, as well as the bicarbonates of the alkali metals. All antacids contain at least one of the following metals: aluminum, calcium, magnesium, sodium, potassium, or bismuth. Antacids help neutralize excess acid produced in the stomach, i.e. the hydrogen ion concentration is reduced.
  - Each antacid has a specific active ingredient. This ingredient whether metallic or nonmetallic has a different effect on the gastric acid. They act similar to when an acid reacts with a hydroxide; a salt and water are produced as in the following equation: **HCl** (aq) **+ NaOH** (aq) **→ NaCl** (aq) **+ H_2O**
  - **Sodium Bicarbonate: HCl** (aq) **+ $NaHCO_3$ (aq) → NaCl** (aq) **+ H_2O + CO_2.**
  - **Calcium Carbonate: HCl** (aq) **+ $CaCO_3$** (aq) **→ NaCl** (aq) **+ H_2O + CO_2.**
  - **Magnesium Compounds: MgO + H_2O → Mg $(OH)_2$; HCl** (aq) **+ Mg $(OH)_2$ → $MgCl_2$ + H_2O**
  - **Aluminum Compounds: $Al(OH)_3$ + HCl → $AlCl_3$ + H_2O**



- ***Side effects of long term antacid therapy:***
  - If pH raises too high rebound acidity to neutralize the alkali occurs.
  - Antacids which absorbed systemically exert alkaline effect on body's buffer system.
  - Some antacids cause constipation (Aluminium containing antacid) while others have laxative effect (Magnesium containing antacid).
  - Sodium containing antacids are problem for patients on sodium restricted diet (for hypertension patient).
  - Antacids containing calcium may cause hypercalcemia, which promotes kidney stones formation and reduces parathormone production.
- ***Requirement of combinations of antacids therapy:***
  - Systemic Antacid leads to alkalosis, may worsen edema and congestive heart failure because of sodium ion load, thereby they are not frequently used.
  - Whereas non-systemic antacid are more potent and effective as compare to systemic antacid, but They are insoluble and poorly absorbed systemically.
  - In Magnesium salt, Magnesium carbonate is most water soluble and reacts with HCl at a slow rate, while Magnesium hydroxide has low solubility and has the power to absorb and inactivate pepsin and to protect the ulcer base.
  - Aluminium hydroxide is a weak and slow reacting antacid. The aluminium ions relax smooth muscles and cause constipation.
  - Calcium carbonate is a potent antacid with rapid acid neutralizing capacity, but on long term use, it can cause hypercalcemia, hypercalciuria and formation of calcium stone in kidney.
  - Every single compound among antacid have some side effect especially when used for longer period or used in elderly patients. To avoid certain side effects associated with antacids, combinations of antacids are used such as:

i. **Magnesium** and **aluminium** containing preparation e.g. magnesium hydroxide a fast acting antacid with aluminium hydroxide which is a slow acting antacid.

ii. **Magnesium** and **calcium** containing preparation where one is laxative and the later one is constipative in nature.

- ***Indications and principles of clinical use:***

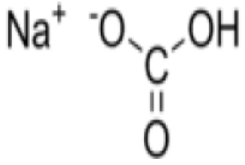
  - **Gastro Esophageal Reflux Disease** (GERD) Antacids neutralize hydrochloric acid, inactivate pepsin, absorb bile acids, stimulate the synthesis of bicarbonates and raise the tone of the lower esophageal sphincter.
  - **Gastric and duodenal ulcers**
  - **Acute and Chronic gastritis / gastroduodenitis**
  - **Gastropathy caused by nonsteroidal anti-inflammatory drugs (NSAIDs - gastropathy):** Antacids can be taken alone or in addition to anti-secretory drugs in order to prevent gastro- and duodenopathies affected by the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Antacids are recommended for healthy people with discomfort or epigastric pain.
  - Antacids are used in the intensive care units to prevent so-called "stress ulcers".

- ***Antacids interaction with other drugs:***

  - Antacids that contain calcium, magnesium and aluminum ions are chelators. They bind a great number of drugs such as digitoxin, tetracycline, indomethacin, aspirin, cimetidine, ranitidine, famotidine, theophylline etc.
  - Antacids also reduce the bioavailability of few drugs like barbiturates, sulfonamides, penicillin.
  - To avoid undesirable interactions, antacids are usually used 2 hours before or after taking any medication.

❖ Sodium bicarbonate

- **Molecular formula** **$NaHCO_3$**
- **Molar mass** **84.01 g/mol**
- **Synonym** Baking soda; Bread soda, Cooking soda, Bicarbonate of soda



▪ Properties

Appearance	**:**	White crystalline power or granules
Odor	**:**	Odourless
Taste	**:**	Saline taste
Density	**:**	1.1 to 1.3 g/cm^3
Melting point	**:**	Decomposes to sodium carbonate starting at 50^0 C
Solubility in water	**:**	*Freely soluble in water*: 69 g/L (0^{0}C); 96 g/L (20^{0}C); 165 g/L (60^{0}C); 236 g/L (100^0 C)
Refractive index	**:**	1.583

▪ Preparation

- $NaHCO_3$ may be obtained by the reaction of carbon dioxide with an aqueous solution of sodium hydroxide. The initial reaction produces sodium carbonate. Further addition of carbon dioxide produces sodium bicarbonate

$$\mathbf{CO_2 + 2\ NaOH \rightarrow Na_2CO_3 + H_2O}$$

$$\mathbf{Na_2CO_3 + CO_2 + H_2O \rightarrow 2\ NaHCO_3}$$

- On an industrial scale it is obtained by Solvay process:

$$\mathbf{CO_2 + H_2O \rightarrow H_2CO_3}$$

$$\mathbf{NH_3 + H_2CO_3 \rightarrow NH_4HCO_3}$$

$$\mathbf{NaCl + NH_4HCO_3 \rightarrow NaHCO_3 + NH_4Cl}$$

▪ Reaction

- Thermal decomposition: Above 50^0 C, sodium bicarbonate gradually decomposes into sodium carbonate, water and carbon dioxide. The conversion is fast at 200^0 C

$$\mathbf{2\ NaHCO_3 \rightarrow Na_2CO_3 + H_2O + CO_2}$$

- Sodium bicarbonate reacts with acetic acid, producing sodium acetate, water, and carbon dioxide.

$$\mathbf{NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2}$$

- Sodium bicarbonate reacts with bases such as sodium hydroxide to form carbonates

$$\mathbf{NaHCO_3 + NaOH \rightarrow Na_2CO_3 + H_2O}$$

- When mercuric chloride solution is added to a solution of sodium bicarbonate a reddish precipitated of mercuric oxide is formed.

$$\mathbf{2\ NaHCO_3 + HgCl_2 \rightarrow 2\ NaCl + H_2O + HgO + 2\ CO_2}$$

▪ Assay

- Weigh accurately 1gm of Sodium bicarbonate and dissolve in 20 ml of water, titrate the solution with 0.5N sulphuric acid using methyl orange as indicator.
- Each ml of 0.5N sulphuric acid ≡ 0.0425gm of $NaHCO_3$

▪ Uses

- It is used as Systemic antacid and in electrolyte replacement.
- It is used as systemic alkalinising agent used in the treatment of metabolic acidosis (increase in acidity).
- Bicarbonate of soda can also be useful in removing splinters from the skin.
- Sodium bicarbonate can be added to local anaesthetics, to speed up the onset of their effects and make their injection less painful.
- Sodium bicarbonate may be used as a buffering agent, combined with table salt, when creating a solution for nasal irrigation.
- 0.1% to 1% Sodium bicarbonate solution used as eye lotion.
- Used removed ear wax and lubricating fluid for contact lenses.
- 5% to 10% Sodium bicarbonate solution used as local applicants for burn, insect bites etc.
- Used in preparation of effervescent formulation.

▪ Sodium bicarbonate side effects

- High doses may cause headache, nausea or irritability.
- Sodium bicarbonate side effects can include **metabolic alkalosis**, edema due to sodium overload, congestive heart failure, hyperosmolar syndrome, hypervolemic hypernatremia, and hypertension due to increased sodium.

Note By:

✓ **Symptoms of Alkalosis** or **metabolic alkalosis:**

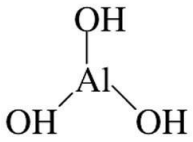
- Confusion(can progress to stupor or coma)
- Hand tremor
- Light-headedness
- Muscle twitching
- Nausea, vomiting
- Prolonged muscle spasms (tetany)

▪ **Dose:** 300 mg to 2 g per day in divided dose.

▪ **Storage:** Store in air tight container.

❖ Aluminum hydroxide gel

- **Molecular formula:** $Al(OH)_3$ - **Molar mass:** 78.00 g/mol
- **Synonym** Hydrated alumina, Ortho Aluminic acid, Aluminic acid
- Aluminium hydroxide is found in nature as the mineral gibbsite (also known as hydrargillite) and its three much rarer polymorphs: BAYERITE, DOYLEITE, and NORDSTRANDITE.



▪ Properties

Appearance	**:**	White amorphous powder
Odor	**:**	Odourless
Taste	**:**	Tasteless
Density	**:**	2.42 g/cm^3
Melting point	**:**	300^{0}C
Solubility	**:**	Practically insoluble in water and alcohol; Soluble in in dilute mineral acid and in solution of alkali hydroxide.
Isoelectric point	**:**	7.7

- Aluminium hydroxide is **amphoteric in nature**, i.e, it has both basic and acidic properties.
- *In presence of an alkali, it behaves as an acid*: $\mathbf{Al(OH)_3 \rightleftharpoons 3H^+ + AlO_3^{3-}}$
- *In presence of an alkali, it behaves as an acid*: $\mathbf{Al(OH)_3 \rightleftharpoons 3OH^- + Al^{3+}}$
- Aluminium hydroxide reacts with acid gives salt and water: $\mathbf{Al(OH)_3 + 3\ HCl \rightarrow AlCl_3 + H_2O}$

▪ Preparation

- It is prepared by hot solution of potash alum slowly with constant stirring to a hot solution of sodium carbonate.

$$\mathbf{3Na_2CO_3 + 2KAl(SO_4)_2 + 3\ H_2O \rightarrow 3\ Na_2SO_4 + K_2SO_4 + 2\ Al(OH)_3 \downarrow + 3\ CO_2 \uparrow}$$

▪ Uses

- Aluminum salts remain in the stomach for long periods and slowly react with stomach acid to form aluminum chloride. Aluminum hydroxide may inhibit the action of pepsin and stimulate stomach mucus secretion.
- Aluminium hydroxide used as gastric antacid.
- Aluminium hydroxide used in treatment of Gastro esophageal reflux disorder.
- ULCER PROTECTIVES: Basic aluminium hydroxide of sulfated sucrose is known as **Sucralfate**, which is used as protective Sucralfate is minimally absorbed after oral administration; action is entirely local. It promotes healing of both duodenal and gastric ulcers. (Sucralfate must be taken before meals)
- In treatment of **Zollinger-Ellison Syndrome**

▪ Aluminium hydroxide side effects

- Constipation
- Osteomalacia (by interfering with PO_4^{3-} absorption)
- Decreased absorption of some drugs (e.g., Tetracyclines and other antibiotics)

▪ Dose

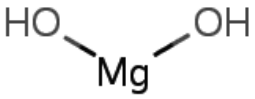
- **Dyspepsia:** 500 to 600 mg orally 4 to 6 times a day as needed, between meals and at bedtime.
- **Gastro Esophageal Reflux Disease, Duodenal and Gastric Ulcer:** 500 to 1500 mg orally 4 to 6 times a day as needed, between meals and at bedtime.

▪ Storage: Store in well-closed containers and should not be allowed to freeze.

- **Zollinger–Ellison Syndrome** is a condition caused by gastrin-secreting pancreatic adenomas that lead to multiple ulcers in the stomach and duodenum.
- **Dyspepsia** is a sensation of pain or discomfort in the upper abdomen.
- **Osteomalacia** softening of the bones, typically through a deficiency of vitamin D or calcium.
- **Osteoporosis** is a disease where increased bone weakness increases the risk of a broken bone.

❖ Magnesium hydroxide

- **Molecular formula:** $Mg(OH)_2$ - **Molar mass:** 58.31 g/mol



- Mg^{2+} Salts or Oxide or Hydroxide acts as both antacids and laxative agents.

▪ Properties

Appearance	**:**	White amorphous powder
Odor	**:**	Odorless
Taste	**:**	Tasteless
Density	**:**	2.34 g/cm^3
Melting point	**:**	350^0 C
Solubility	**:**	Insoluble in water
Refractive index	**:**	1.55

▪ Preparation

- Combining a solution of many magnesium salts with basic water induces precipitation of solid $Mg(OH)_2$:

$$\mathbf{Mg^{2+} + 2\ OH^- \rightarrow Mg(OH)_2}$$

- On a commercial scale, $Mg(OH)_2$ is produced by treating seawater with lime [$Ca(OH)_2$].

$$\mathbf{Mg^{2+} + Ca(OH)_2 \rightarrow Mg(OH)_2 + Ca^{2+}}$$

- **Laboratory Preparation:** $\mathbf{MgCO_3 + 2\ NaOH \rightarrow Mg(OH)_2 + Na_2CO_3}$

▪ Uses

- Used as weak antacid and laxative.
- Most commonly used antacids combine aluminum hydroxide and magnesium hydroxide. The combination decreases the adverse effects of diarrhea (with magnesium products) and constipation (with aluminum products). Calcium carbonate is effective in relieving heartburn, but it is infrequently used to treat peptic ulcers or GERD.

▪ Magnesium hydroxide side effects

- Antacids with magnesium are contraindicated in renal disease because hypermagnesemia may result; those with high sugar content are contraindicated in diabetes mellitus.

❖ Milk of Magnesia

- Milk of Magnesia is a suspension of Magnesium Hydroxide.
- Milk of Magnesia, Double-Strength Milk of Magnesia, and Triple-Strength Milk of Magnesia contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $Mg(OH)_2$, the labeled amount being 80, 160, and 240 mg of $Mg(OH)_2$ per mL, respectively as per **USP Monographs.**
- ***Packaging and storage***: Preserve in tight containers, preferably at a temperature not exceeding 35^{0}C . Avoid freezing.
- **Labeling:**
  - **(i)** Double- or Triple-Strength Milk of Magnesia is so labeled, or may be labeled as **2×** or **3×** Concentrated Milk of Magnesia, respectively.
  - **(ii)** "SHAKE WELL BEFORE USED"
- **Uses:**
  - Milk of Magnesia is used for a short time to treat occasional constipation, it is used as Laxative.
  - Milk of Magnesia is also used to treat symptoms caused by too much stomach acid such as heartburn, upset stomach or indigestion.