Lecture No:4 [Theoretical]

Inorganic Pharmaceutical Chemistry

3rd stage / 1st semester

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❖ Aluminum

3) Antacids

- The function of antacids is to neutralize excess stomach acid.

- They also exhibit cytoprotective effects towards attacks against the gastric mucosa. They are additionally known to heal gastric and duodenal ulcerations; nevertheless, the mechanism is still uncertain.

- Antacids have been in use for the past 2000 years, and the initial formulations were based on CaCO3 (coral and limestone). Nowadays, the antacid/anti-gas market is a significant income stream for the pharmaceutical industry and the demand for antacids is expected to grow.

- The number of people suffering from heartburn increases with an ageing population, more stressful lifestyles and changing eating habits such as eating out more often.

- Aluminum hydroxide ($Al(OH)_3$) has several medical applications. It is used as an antacid for treating heartburn as well as acid indigestion (reflux esophagitis). It is also known to have healing properties of peptic ulcers.

- In patients suffering from kidney failure, who show elevated serum phosphate levels (hyper- phosphataemia), $Al(OH)_3$ is used as a phosphate binder.

- $Al(OH)_3$ is an amphoteric compound, which means it can react as a base or as an acid. In its application as an anti-acid, $Al(OH)_3$ reacts with any excess stomach acid (mainly HCl) with the formation of $AlCl_3$ and water.

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$$

- $Al(OH)_3$ is known to cause constipation, so formulations of anti-acids often include a combination with Mg^{2+} antacids. Usually, oral antifoaming agents, such as simethicone, are added to reduce bloating and discomfort/pain.

- Simethicone is a mixture of poly(dimethyl siloxane) and silica gel, which decreases the surface tension of gas bubbles.

Table 4.2 *Typical formulation of an antacid/antigas mixture (maximum strength Maalox®, Max®, Norvatis)*

Active ingredient	Quantity (mg)	Purpose
$Al(OH)_3$	400	Antacid
$Mg(OH)_2$	400	Antacid
Simethicone	40	Anti-gas

- Ancient anti-acid formulations contained sodium bicarbonate (baking soda, $NaHCO_3$), which resulted in a rapid reaction with the gastric acid. The result was an increase in the gastric pH and the production of CO_2 gas as a by-product.

- Large doses of $NaHCO_3$ can cause alkaline urine and this can result in kidney problems. Acid neutralization using $Al(OH)_3$ does not produce CO_2 and therefore these side effects can be avoided.

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

- Aluminum glycinate $[Al(NH_2CH_2COO)(OH)_2]$ is also used in anti-acid formulations. For example, Gastralgine® contains, amongst other ingredients, dihydroxy aluminum glycinate $[Al(NH_2CH_2COO)(OH)_2]$, $Al(OH)_3$, magnesium trisilicate and simethicone. It is known to have additionally protective effects from ulcers.

4)Antiperspirant

- Aluminum trichloride ($AlCl_3$) was the first compound that was used as an antiperspirant.
- The mechanism of action is still under investigation, but it appears to act by forming a plug of $Al(OH)_3$ within the sweat duct.
- $AlCl_3$ is a very strong antiperspirant and only advised by doctors if normal antiperspirants do not work.
- Leading brands of antiperspirants contain usually a ~20% aluminum hexahydrate solution in an alcoholic base.
- It is thought to work by blocking the openings of the sweat ducts. It tends to work best in the armpits. However, it may also work for sweating of the palms and soles. It can also be applied to the face, taking care to avoid the eyes.

❖Gallium

1)Introduction

- Gallium has atomic number 31 in the periodic table of elements.
- It has a silvery-white color with a melting point of only 29 ∘C, which means that it melts when held in the hand.
- It has no known physiological role in the human body, but it can interact with cellular processes and proteins that are normally involved in iron metabolism.
- Gallium tartrate has a long research history. Researchers showed in the 1930s that it could be used to treat syphilis in rabbits with no significant toxicity.

- In subsequent studies, it has been shown that gallium ions predominantly accumulate in the bone and therefore would be a good candidate for radiotherapy of bone cancer.

- Unfortunately, the radioactive isotope ^{72}Ga has only a half-life of around 14 h, which is not long enough for effective radiotherapy.

- Nevertheless, current clinical developments involve the use of radioactive gallium isotopes as tumor imaging reagents, gallium nitrate in metabolic bone disease, hypercalcemia, and as anticancer drug, as well as up-to-date research in chemotherapeutic applications.

2)Chemistry

- Gallium exists as the trivalent cation Ga^{3+}, and in aqueous solution it presents as a hydrated complex.
- Depending on the pH, a variety of hydroxyl species are formed, some of which are insoluble, such as $Ga(OH)_3$.
- At physiological pH, nearly no free Ga^{3+} is present and the hydroxyl species $Ga(OH_4)^-$ (gallate, the dominant species) and $Ga(OH)_3$ are formed.

- Gallium hydroxide species are amphoteric, analogous to aluminum hydroxide compounds.
- It is important to note that the stability of solutions containing gallium chloride or gallium nitrate for oral administration is affected by the pH.
- They might not be stable over extended periods and gallium hydroxide precipitates.

3) Pharmacology of gallium-based drugs

- Ga^{3+} has an ionic radius and binding properties like those of Fe^{3+} (ferric iron). Unlike Fe^{3+}, it cannot be reduced to its divalent state, which means that it follows a completely different redox chemistry compared to iron.

- The oxidation and reduction of iron is important in many biological processes, which therefore cannot be mimicked by gallium.

- One example includes the uptake of Fe^{2+} by the haeme group. As Ga^{3+} is not readily reduced to it +II state, it cannot bind to the haeme group.

- Transferrin is an important transport protein that controls the level of free Fe^{2+} in the blood plasma.

- Free iron ions are toxic to most forms of life, and therefore transferrin binds Fe^{2+} and removes it from the blood. There is an excess of transferrin present in the blood, and it has been shown that Ga^{3+} can also bind to this glycoprotein but with a lower affinity than Fe^{3+}.

- Once the binding capacity of gallium ions to transferrin is exceeded, it is believed to circulate as gallate [$Ga(OH)^{4-}$].

- The therapeutic action of Ga^{3+} is very much based on the pharmacological activity of Fe^{3+} which it mainly mimics.

- Ribonucleotide reductase has been proposed as the main target for Ga^{3+}. Binding to this enzyme will impair DNA replication and ultimately lead to apoptosis. *In vitro* studies have shown that Ga^{3+} can bind directly to DNA.

- Ga^{3+} is transported via transferrin to areas of the body that require increased Fe^{3+} levels, including proliferating cancer cells.

- Ga^{3+} can interrupt the cell cycle and DNA synthesis by competing with iron for the active sites in essential enzymes.

- Ga^{3+} accumulates in the endosomes mediated by transferrin uptake and transported into the cytosol, where it can bind to the enzyme ribonucleotide reductase.

4) Gallium nitrate – multivalent use

- In clinical trials, gallium nitrate has proved to be highly active as an antitumor agent especially against non-Hodgkin’s lymphoma and bladder cancer.

- The cytotoxic activity of gallium nitrate has been demonstrated as single agent and as part of combination therapy, for example, together with fluorouracil.

- Gallium nitrate shows a relatively low toxicity and does not produce myelosuppression, which is a significant advantage over other traditional anticancer agents.
- Furthermore, it does not appear to show any cross-resistance with conventional chemotherapeutic agents.
- These studies have also shown that gallium nitrate is able to decrease serum calcium levels in patients with tumor-induced hypercalcemia.

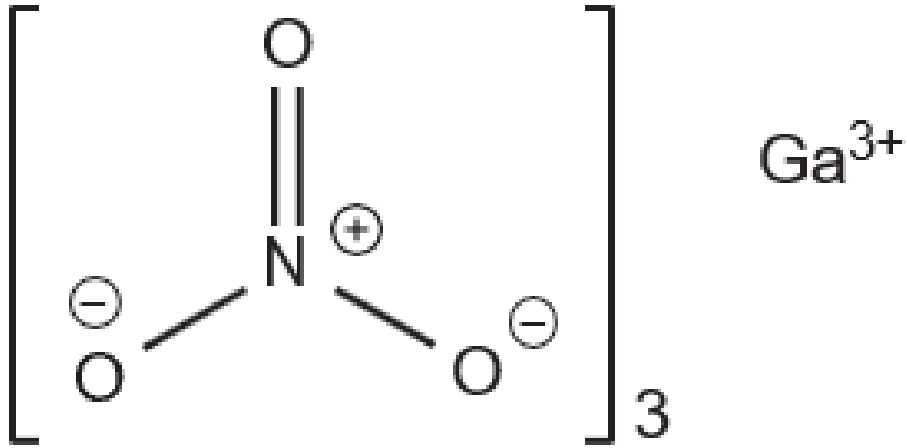

***Figure 8** Gallium nitrate*

- Subsequently, several studies have been carried out comparing traditional bisphosphonate drugs with gallium nitrate in their ability to decrease the calcium levels that are elevated as a result of cancer.

- Based on the clinical efficacy, gallium nitrate injections (Ganite™) was granted approval by the FDA for the treatment of cancer-associated hypercalcemia.

- Gallium nitrate is also believed to inhibit the bone turnover and therefore to decrease osteolysis, the active reabsorption of bone material, in patients with bone metastasis secondary to other cancers.

5) Gallium 8-quinolinolate

- Gallium 8-quinolinolate is a hexacoordinated Ga^{3+} complex in which the central gallium atom is coordinated by three quinolinolate groups.

- It was developed as an orally available anticancer agent. It was successfully tested in vitro against lung cancer and in transplanted rats against Walker carcinosarcoma.

- Main side effects were detected in experiments on mice at doses of 125 mg/kg/day. These included leukopaenia and some fatalities. The highest concentrations Ga^{3+} were found in the bone, liver and spleen.

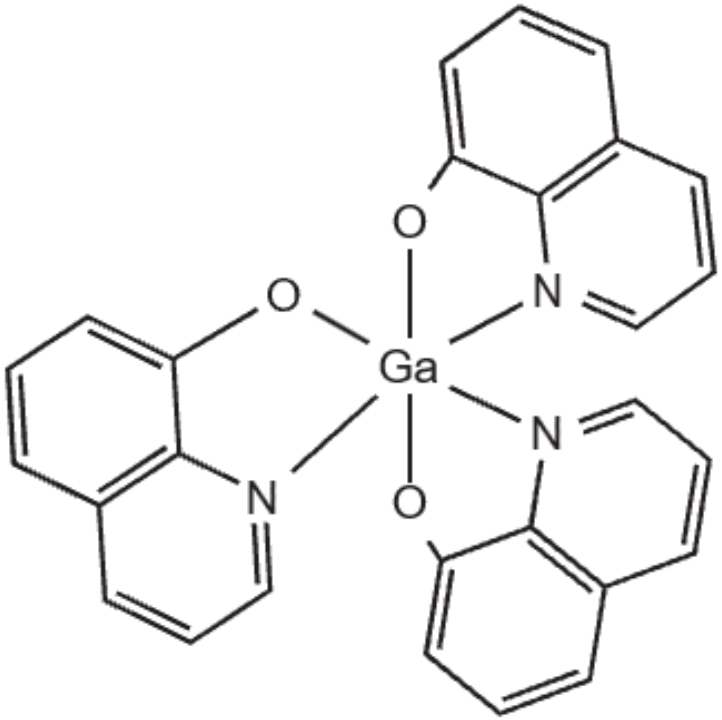

Figure 9 *Chemical structure of gallium 8-quinolate*

- Preclinical studies have established the IC_{50} values for a single-agent activity in the lower micromolar range for a variety of cancer cell lines.

- These cell lines include human lung adenocarcinoma, where gallium 8-quinolinolate was shown to be 10 times more potent than gallium nitrate. Other cell lines include melanoma and ovarian, colon and breast cancer. The inhibitory effect appears to be dose dependent and not time dependent.

- Gallium 8-quinolinolate entered phase I clinical trials under the drug name KP46 in 2004 to establish its safety and toxicity profile.

- KP46 was orally administered as a tablet, containing 10 – 30%w/w. Dose up to 480 mg/m^2 were given to patients with advanced solid malignant tumors. The drug was well tolerated and preliminary success was seen in patients with renal cell cancer.

6) Gallium maltolate

- Gallium maltolate [tris(3-hydroxy-2-methyl-4*H*-pyran-4-onato)gallium(III)] is a coordination complex containing a central Ga^{3+} ion and three maltolate (deprotonated maltol) groups.

- Clinical studies have shown that oral administration of gallium maltolate leads to significantly increased bioavailability compared to gallium chloride. The oral bioavailability is estimated to 25 – 57% in comparison to 2% for gallium chloride.

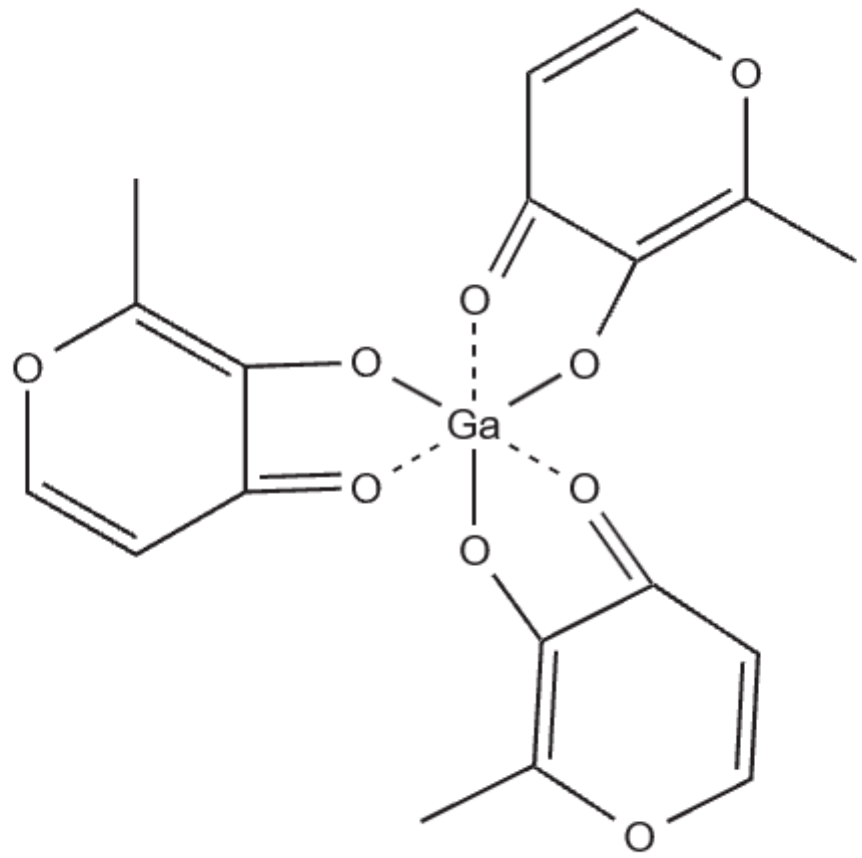

Figure 10 *Chemical structure of gallium maltolate*

- Phase I clinical trials on healthy humans showed that doses were well tolerated up to 500 mg. Further- more, the results suggested the possibility of a once-per-day treatment option because of the half-life of the drug in the blood plasma (17 – 21 h).

- Orally administered gallium maltolate is excreted significantly more slowly via the kidneys than gallium nitrate injected intravenously.

- It has been proposed that rapid intra- venous administration leads to the formation of gallate, which is quickly cleared as a small molecule via the kidneys. In contrast, oral administration leads to a slow loading of the blood plasma, and Ga^{3+} is bound to transferrin.

- This may lead to a different mechanism of excretion, leading to a reduction in renal toxicity. Also, the transferrin-bound Ga^{3+} has the potential to be directly transported to the cancer cell without causing significant side effects. Therefore, an oral administration seems to be superior to parenteral administration.