M.Sc. Chemistry

(Core Course- XI)

Bio-Inorganic Chemistry

Unit- V Metal in Medicine

[Introduction, Alkali and Alkaline earth metals as drug, pharmaceutical application of boron and aluminium compounds, transition metal complexes as potential medicinal agent, Radioactive compounds and their clinical applications, Chelation therapy.]

Q-what is inorganic molecules? and how they used in pharma industries?

- The first important synthetic inorganic compound was ammonium nitrate for soil fertilization. Inorganic compounds are found in nature as minerals.
- Soil contains iron sulfide as pyrite or calcium sulfate as gypsum. They are also found multitasking as biomolecules: As electrolytes (sodium chloride), in energy storage (ATP) or in construction (the polyphosphate backbone in DNA).
- Inorganic compounds are synthesized for use as drugs such as cisplatin, magnesium hydroxide, catalysts such as vanadium (V) oxide and titanium (III) chloride, or as reagents in organic chemistry such as lithium aluminium hydride.

Inorganic pharmaceuticals are useful in some of the following ways.

1. Useful medicinally for their therapeutic purpose. Example: Astringents and antimicrobials etc.
2. Useful as pharmaceutical aids. Example: Bentonite, talc etc.
3. To change the reaction of body fluid. To acidify or alkalise. Example: Antacids, alkalis, mineral acids.
4. Replacing or replenishing the normal content of body fluids. Example: Sodium, potassium, calcium, chloride, phosphate etc.
5. Useful as reagents to carry out the reactions. Example: Catalysts (platinum, nickel) oxidizing and reducing agents (lithium aluminium hydride).
6. Useful in Pharmaceutical analysis. Example: Titrants such as potassium permanganate etc.

Q- Why use metal-based drugs? Define some terminology exhibit by metal-based drugs.

- Metal complexes exhibit unique properties, which allow metal ions to interact with biomolecules in a unique way and, on the other, allow scientists to safely administer even toxic metal ions to the human body.
- Coordination, redox, magnetic, and radioactivity are the unique properties displayed by metal centres together with the high aqueous solubility.
- The ability to be involved in reduction and oxidation reactions has led to the use of metal complexes in photodynamic therapy (PDT). Transition metals are able to coordinate to electron-rich biomolecules such as DNA. This can lead to the deformation of DNA and ultimately to cell death. Therefore, some transition metals act as potential anticancer agents.
- Metals that display a magnetic moment can be used as imaging reagents in magnetic resonance imaging (MRI). Many metals have radioactive isotopes, which can be used as so-called radiopharmaceuticals for therapy and radio imaging.

Adjuvant: An adjuvant is an agent or a mixture of agents that possesses the ability to bind to a specific antigen.

Antibacterial: Drugs which are used in the treatment of bacterial infections. Example: Yellow mercuric oxide (ophthalmic).

Antifungal agents: Drugs which are used in the treatment of fungal infections. Example: Zinc undecylenate (topical use), Potassium iodide.

Antiseptics: Drugs which are used to inhibit the growth and development of micro-organism without killing. Example: Strong iodine solution.

Antacids: These are drugs which are usually alkaline substances, used for neutralizing excess acid in the stomach. Example: Aluminium hydroxide gel, Calcium carbonate, Magnesium carbonate.

Antiperspirant: Drugs which are used to remove the bad odour in body. Example: Aluminium sulphate.

Astringents: These are the substances which bring about protein precipitation. Astringent action is evidenced by contraction and wrinkling of tissue and by blanching. Example: Calamine, Aluminium citrate.

General anaesthetics: Drugs which are used to produce reversible loss of sensation. Example: Nitrous oxide.

Iodine supplements: Drugs which are used in the treatment of iodine deficiency. Example: Potassium iodide.

Laxatives: Drugs which are used to promote the evacuation of bowel. Example: Magnesium Sulphate, Sodium phosphate.

Radiotherapeutic agents: Radioisotopes used for the treatment of diseases. Example: isotopes of Iodine, Strontium.

Q- Alkali earth metals as drug.

Developments and pro-cons of lithium-based drugs

- The first medical use of Li+ was described in 1859 for the treatment of arthritis and gout (uric acid crystal generation). The theory at that time was based on the ability of lithium to dissolve nitrogen-containing compounds such as uric acid. Their build-up in the body was believed to cause many illnesses such as rheumatic conditions and gout problems.
- In 1880, Li+ was first reported as being used in the treatment of bipolar disorder, and in 1885 lithium carbonate ($Li2CO_3$) and lithium citrate [$Li_3C_3H_5O(COO)_3$] were included in the British Pharmacopoeia.
- Lithium salts are used in the prophylaxis and treatment of mania, and in the prophylaxis of BD and recurrent depression. Lithium therapy is taken orally, usually as lithium carbonate ($Li2CO_3$) or lithium citrate [$Li_3C_3H_5O(COO)_3$], with a total dose of up to 30 mmol/day. Li_2CO_3 is the preferred lithium salt used, as it causes the least irritation to the stomach. The treatment has to be closely monitored, and Li+ blood concentrations are measured 12 h after administration to achieve a serum lithium concentration of 0.4–1 mmol/l.
- The therapeutic index (concentration window from efficacy to toxicity) for Li+ is very narrow, and plasma Li^+ concentrations above 2 mM require emergency treatment for poisoning.
- The specific mode of action of the simple Li^+ ion is currently unknown, but it is clear that a displacement of Mg^{2+} by Li^+ is involved. Therefore, an alteration of the Mg^{2+} balance in the blood and the urine can be observed in patients treated with Li+ [3b]. This displacement is actually not surprising because the properties of Li+ and Mg^{2+} are similar, which can be explained by the concept of diagonal relationship (see Section 2.2.4).
- LiCl was prescribed as replacement for NaCl in the diet of affected patients for heart related dieses. The urea hypothesis and the connection of NaCl to heart diseases stimulated the use of lithium salts

in common food. The prime example is the soft drink 7Up, which has been marketed in 1929 under the label Bib-Label Lithiated Lemon-Lime Soda contained lithium citrate.

- The actual Li+ was subsequently removed in 1950. John Cade's experiments on guinea pigs in 1949 initiated the discovery of Li+ and its sedative and mood-control properties.
- Uric acid was known to have mood-controlling properties and Cade used lithium urate as a control solution. To his surprise, he discovered that lithium urate had tranquillising properties, and after further experiments he concluded that this was caused by the lithium ion. Nevertheless, there were drawbacks, especially when the FDA banned Li+ salts following the death of four US patients. These patients had an average intake of 14 g of lithium chloride (LiCl) per day in order to replace NaCl.
- Another stumbling stone in the way of success of Li+ was the discovery of chlorpromazine, the first antipsychotic drug, which is still used for the treatment of BD. In the early 1970s, Li+ was re-approved by FDA and is now used in 50% of the treatment of BD [5].

Isotopes of lithium and their medicinal application.

- Lithium occurs as mixture of two stable, naturally occurring isotopes, as ^{6}Li (7.59%) and the major isotope ^{7}Li (92.41%). The nucleus of 6Li contains three protons and three neutrons, whilst 7Li contains three protons and four neutrons. 6Li and 7Li are both NMR active nuclei, which means their presence can be monitored via NMR technology.
- Using this analytical tool, it is possible to differentiate between intra- and extracellular Li+ concentrations and therefore, the uptake of Li+ into different cells can be monitored.
- The use of 6Li results in sharper NMR spectra because of its properties, but it also has a lower intensity. 6Li salts can also be used to monitor the distribution of lithium in the tissue. A further application of 6Li is the production of tritium atoms (3H1) and their use in atomic reactors.

In this process, 6Li is bombarded with neutrons, which results in the production of tritium atoms and radioactive α-particles (4He2):

$$^{6}_{3}\mathrm{Li} + ^{1}_{0}\mathrm{n} \rightarrow ^{3}_{1}\mathrm{H} + ^{4}_{2}\mathrm{He}$$

Sodium: an essential ion in the human body.

- Sodium has atomic number 11 and has the symbol Na, derived from the Latin name 'natrium'. Na^+ is also part of minerals and an essential element for all animal life.
- The main biological roles of sodium ions are the maintenance of body fluids in humans and the functioning of neurons and transmission of nerve impulses.
- Na^+ is an important electrolyte and a vital component of the extracellular fluid. Therefore, one of its roles is to maintain the fluid in the human body via osmoregulation, a passive transport mechanism.
- Na^+ ions also play a crucial role in the contraction of muscles and in the mode of action of several enzymes. In the human body, Na^+ is often used to actively build up an electrostatic potential across membranes, with potassium ions (K^+) being the counter-ion.
- The build-up of an electrostatic potential across cell membranes is important to allow the transmission of nerve impulses.
- Sodium chloride solutions are normally used when the patient is diagnosed with sodium depletion and dehydration. Treatment is mostly administered intravenously, but in chronic conditions (mild to moderate sodium loss) sodium chloride or sodium bicarbonate can be given orally. Oral rehydration therapies usually use a mixture of alkali metal-based salts such as NaCl, KCl and their citrates.
- Sodium bicarbonate is usually administered orally in order to regulate the serum pH. Imbalances of the plasma pH can be due to problems occurring in the kidneys such as renal tubular acidosis.
- The maximum salt intake is recommended to be limited to 6 g of NaCl for an adult, whereas intake for children should be significantly lower.

- the high salt plasma levels (hypernatraemia) can result in cardiovascular disorders such as hypertension. Low sodium results into low blood pressure, dehydration and muscle cramps are signs of a sodium deficiency.

Potassium and its clinical application.

- Potassium was first isolated from potash, which is potassium carbonate (K_2CO_3). Potassium occurs in nature only in the form of its ion (K+) either dissolved in the ocean or coordinated in minerals because elemental potassium reacts violently with water.
- Potassium ions are essential for the human body and are also present in plants. The major use of K+ can be found in fertilisers, which contains a variety of potassium salts such as potassium chloride (KCl), potassium sulfate (K_2SO_4) and potassium nitrate (KNO_3).
- KCl is also found in table salt, whereas potassium bromate ($KBrO_3$) is an oxidising agent and is used as flour improver. Potassium bisulfite ($KHSO_3$) can be used as a food preservative in wine and beer.
- Hypokalaemia is a potentially serious condition where the patient has low levels of K+ in his/her blood plasma. Symptoms can include weakness of the muscles or ECG (electrocardiogram) abnormalities. Mostly, hypokalaemia can be a result of reduced K+ intake caused by GI disturbance, such as diarrhoea and vomiting, or increased excretion of K+ caused by diuresis. Oral supplementation will be provided to the patient.
- Potassium citrate is used to treat mild urinary-tract infections by increasing the urinary pH. It should be not given to patient if they experience pain in the kidney area (risk of kidney stones) or if blood or pus is present in the urine. Also, patients with raised blood pressure or diabetes should avoid taking potassium citrate without consultation with their general practitioner (GP).

Q- Alkaline earth metals as drug.

- In terms of clinical use, magnesium and calcium are essential ions for the human body and any of their imbalances should be corrected. Strontium is medically used in radiotherapy.
- Exposure to excess beryllium can lead to the so-called chronic beryllium disease (CBD), which is discussed later in this chapter. Barium salts are generally highly toxic. Nevertheless, the so-called barium meal is a well-used oral radio-contrast agent.

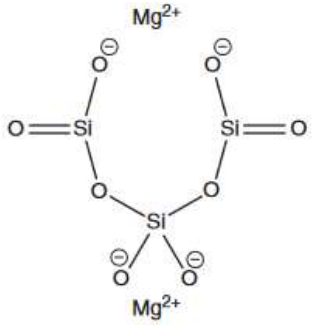
Beryllium and chronic beryllium disease (CBD)

- Beryllium and its compounds are extremely poisonous and therefore there is very few clinical applications.
- The inhalation of beryllium or its compounds can lead to serious respiratory diseases such as the chronic beryllium disease, and soluble beryllium compounds can cause serious skin irritations.
- Workers within the metal production industry are most likely exposed to beryllium and run the highest risk of developing CBD. Symptoms are not well reported, may occur many years after the exposure and include cough, fatigue and chest pain, whereas non respiratory organs can also be affected.

Clinical applications and preparations of Mg

- Most magnesium salts are soluble in water and given in large amounts to work as a laxative in the human body.
- Magnesium ion imbalances can manifest in a variety of conditions such as hypo- and hypermagnesemia.
- Magnesium salts are involved in the treatment of arrhythmia (irregular heartbeat) and eclampsia (high blood pressure, headaches), a life-threatening hypertensive disorder in pregnant women.
- Mg^{2+} ions are initially given as I.V. or intramuscular injection. $MgSO_4$ can also be used as emergency treatment for very serious arrhythmias, a disorder of the heart rate (pulse).

- The 'milk of magnesia' is a suspension of $Mg(OH)_2$ in water, which has a milk-like appearance because of the low aqueous solubility of Mg(OH)2. It is considered as a strong electrolyte and a weak base and is given to the patient for indigestion and heartburn. The alkaline suspension neutralises any excess stomach acid and therefore works as an antacid. Magnesium trisilicate ($Mg_2Si_3O_8$) can also be used in antacid preparations especially in the treatment of peptic ulcers.



- The mode of action includes the increase of the pH of the gastric fluid together with the formation of a colloidal silica precipitate, which forms a protection for the GI mucosa. Most antacids contain a mixture of aluminium hydroxide [$Al(OH)_3$] and magnesium and/or calcium preparations.
- The antacids reduce the absorption of the simultaneously taken drug. Therefore, before any treatment with antacids, the full medical history of the patient should be taken, and possible interactions assessed.

Clinical application of Ca

- Calcium supplements are usually required only if the dietary Ca_{2+} intake is insufficient. The dietary requirements depend on the age and circumstances. In severe acute hypocalcaemia, a slow I.V. injection of a 10% calcium gluconate has been recommended.
- A variety of calcium salts are used for clinical application, including **calcium carbonate**, **calcium chloride**, **calcium phosphate**, **calcium lactate**, **calcium aspartate** and **calcium gluconate**.
  Structure (H.W.)

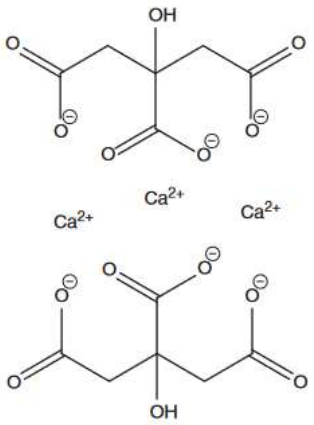


Figure 3.11 Chemical structure of calcium citrate

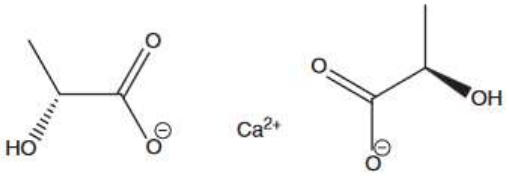


Figure 3.12 Chemical structure of calcium lactate

- Calcium carbonate is the most common and least expensive calcium supplement. It can be difficult to digest and may cause gas in some people because of the reaction of stomach HCl with the carbonate and the subsequent production of CO2.
- Taking magnesium salts with it can help prevent constipation. Calcium carbonate consists of 40% Ca2+, which means that 1000 mg of the salt contains around 400 mg of Ca2+.
- Calcium citrate is more easily absorbed. It is easier to digest and less likely to cause constipation and gas than calcium carbonate. Calcium citrate can be taken without food and is more easily absorbed than calcium carbonate on an empty stomach. It is also believed that it contributes less to the formation of kidney stones. Calcium citrate consists of around 24% Ca2+, which means that 1000 mg calcium citrate contains around 240 mg Ca2+.
- The properties of calcium lactate are similar to those of calcium carbonate, but the former is usually more expensive. Calcium lactate contains effectively less Ca2+ per gram salt than, for example, calcium carbonate. Calcium lactate consists of only 18% Ca2+, making it a less 'concentrated' salt.
- Calcium gluconate is prescribed as a calcium supplement, but it is also used in the urgent treatment of hyperkalaemia. Hyperkaleamia in the presence of ECG changes usually requires immediate treatment, and a 10% calcium gluconate solution intravenously administered is recommended.

- Calcium gluconate contains effectively the least Ca^{2+} per amount of supplement (only around 9%). That means that in 1000 mg calcium gluconate, only 90 mg is actual Ca^{2+}.

Clinical application of Ba

- The clinical use of barium sulphate suspension is well known under the term barium meal. Patients are given a suspension of barium sulfate to swallow. Using X-ray imaging, the whole GI track can be visualised.
- The heavy barium ions absorb X-rays readily and therefore these structures become visible in an X-ray screening. Barium sulfate is a well-used and tolerated oral radio-contrast agent.

Application of Zinc in Medicinal area

Zinc (Zn) is an essential trace element with important roles in enzyme function, immune response, and cellular signalling. Due to its biocompatibility and low toxicity, zinc and its compounds have been promoted for various therapeutic applications.

Drug Formulation & Stabilization

- Used in insulin preparations (e.g., zinc-insulin hexamers in long-acting insulin analogs like insulin glargine). Stabilizes proteins and vaccines by preventing degradation.

Antimicrobial & Antiviral Agents

- Zinc oxide (ZnO) nanoparticles in wound dressings, antiseptic creams, and sunscreens. Zinc pyrithione in antidandruff shampoos (e.g., Head & Shoulders®). Zinc lozenges for reducing cold symptoms (inhibits rhinovirus replication).

Therapeutic Supplements

- Zinc sulfate/gluconate tablets for zinc deficiency and diarrhea treatment (WHO-recommended).Zinc acetate (Galzin®) for Wilson's disease (blocks copper absorption).

Cancer & Neurodegenerative Research

- Zinc-thiosemicarbazone complexes show anticancer activity. Zinc chelators (e.g., clioquinol) tested for Alzheimer's disease.

Nanomedicine & Drug Delivery

- ZnO nanoparticles enhance drug delivery and antibacterial efficacy.Used in bioactive coatings for implants.

Advantages

- Low toxicity compared to other metals (e.g., platinum, copper).
- Cost-effective and abundant.
- Multifunctional (antimicrobial, anti-inflammatory, stabilizing agent).

Pharmaceutical applications of boron and Aluminium Compounds

Pharmaceutical applications of boric acid

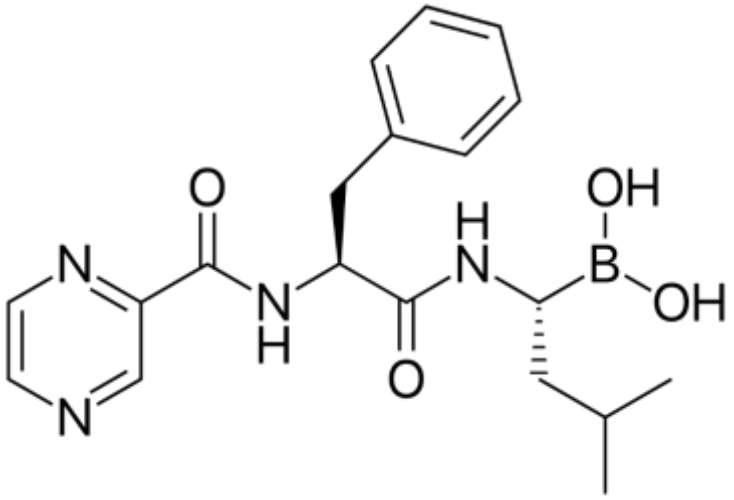
- Boric acid is a long-standing traditional remedy with mainly antifungal and antimicrobial effects. For medicinal uses, it has become known as sal sedativum, which was discovered by Homberg, the Dutch natural philosopher, in 1702.
- Diluted solutions were and sometimes still are used as antiseptics for the treatment of athletes' foot and bacterial thrush, and in much diluted solutions as eyewash. Boric acid can be prepared by reacting borax with a mineral acid:

  $Na_2B_4O_5(OH)_4.8H_2O + 2HCl \rightarrow 4B(OH)_3[\text{or } 4(H_3BO_3)]+2NaCl + 5H_2O$
- In general, there are many other health claims around the clinical use of boric acid and boron-containing compounds, but many of those have no supporting clinical evidence.

Bortezomib

- Bortezomib belong to the class of drugs called proteasome (Hydrolysis of protein) inhibitors and is licensed in the United States and the United

Kingdom for the treatment of multiple myeloma (Cancer which produce white blood cell).



- The drug has been licensed for patients in whom the myeloma has progressed despite prior treatment or where a bone marrow transplant is not possible or was not successful.
- It is marketed under the name Velcade® or Cytomib®. Velcade is administered via injection and is sold as powder for reconstitution. Bortezomib was the first drug approved in the new drug class of proteasome inhibitors and boron seems to be its active element.
- For the mode of action, it is believed that the boron atom binds with high affinity and specificity to the catalytic site of 26S proteasome and inhibits its action.
- Therapy with Bortezomib can lead to a variety of adverse reactions, including peripheral neuropathy, myelosuppression, renal impairment and gastrointestinal (GI) disturbances together with changes in taste.

Aluminium-based adjuvants

- An adjuvant is an agent or a mixture of agents that possesses the ability to bind to a specific antigen. Adjuvants are added to vaccines to increase the antibody responses to the vaccination and/or to stabilise the preparation.
- Adjuvants can absorb many antigenic molecules over a wide surface area, thus enhancing the interaction of immune cells with the

presenting antigens and leading to an increase of the immune response stimulation.

- Aluminium-based adjuvants have a long-standing tradition and have been used for more than 50 years. They are the most widely used adjuvants in human and veterinary vaccines licensed by the FDA.
- Some adjuvants can function as a slow-release delivery system. They trap the antigen at the injection site. From there, the antigen is slowly released, which causes a steady stimulation of the immune system.
  Ex. Anthrax vaccine, hepatitis A, hepatitis B.
- The adjuvant effect of potassium alum ($KAl(SO4)2{\cdot}12H2O$) was first discovered in 1926. Researchers examined diphtheria toxoids precipitated with alum and were able to show that an injection of this alum precipitate led to a significant increase in immune response.
- Subsequent research showed that aluminium hydroxide ($Al(OH)3$) hydrogels can be pre-formed in a standardised manner and be used to absorb protein antigens to form a homologous preparation. These vaccines are called aluminium-absorbed vaccines and, in contrast to alum-precipitated vaccines, the antigens are distributed homogeneously.
- Typical adjuvants are alum [$KAl(SO4)2{\cdot}12H2O$], $Al(OH)3$, $AlPO4$, $Al2O3$, but oxides of other metals, such as $ZrO2$,$SiO2$ and $Fe2O3$, are also under investigation.
- The formation of the aluminium hydrogels is generally achieved by reacting $Al3+$ ions (from compound such as $AlCl3$) under alkaline aqueous conditions. Conditions are strongly regulated, as even smallest changes to parameters such as temperature, concentration and others can influence the quality of the hydrogel.
- Aluminium phosphate gels are typically produced by reacting $Al3+$ salts in the presence of phosphate ions under alkaline conditions.
- The mode of action suggest by research is that antigens need to be adsorbed to the adjuvant before the immunisation reaction. It is believed that the adjuvant will then present the antigen to the immune component of the targeted cell.

Antacids

- The function of antacids is to neutralise excess stomach acid. They also exhibit cytoprotective effects towards attacks against the gastric mucosa. They are additionally known to heal gastric and duodenal ulcerations.
- 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.
- Aluminium hydroxide (Al(OH)3) has several medical applications. It is used as an antacid for treating heartburn as well as acid indigestion (reflux oesophagitis). It is also known to have healing properties of peptic ulcers. In patients suffering from kidney failure, who show elevated serum phosphate levels (hyperphosphataemia).
- 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 AlCl3 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 Mg2+ antacids and simethicone 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. 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 neutralisation using $Al(OH)_3$ does not produce CO2 and therefore these side effects can be avoided.
- Aluminium glycinate [$Al(NH_2CH_2COO)(OH)_2$] is also used in anti-acid formulations. For example, Gastralgine® contains, amongst other ingredients, dihydroxy aluminium glycinate [$Al(NH_2CH_2COO)(OH)_2$], $Al(OH)_3$, magnesium trisilicate and simethicone.

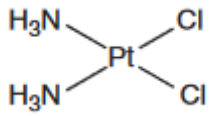
Antiperspirant (Remove bad smell from body)

- Aluminium 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% aluminium 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.

Transition Metal as Medicine

Cisplatin

- cisplatinum or cisplatin also referred as CDDP, is a yellow powder and widely used as chemotherapeutic agent. The platinum complex binds to DNA and causes cross-linking, which triggers the programmed cell death (apoptosis).
- Cisplatin is specifically used as an effective therapeutic agent against ovarian, testicular, uterus, bladder and head and neck cancers.



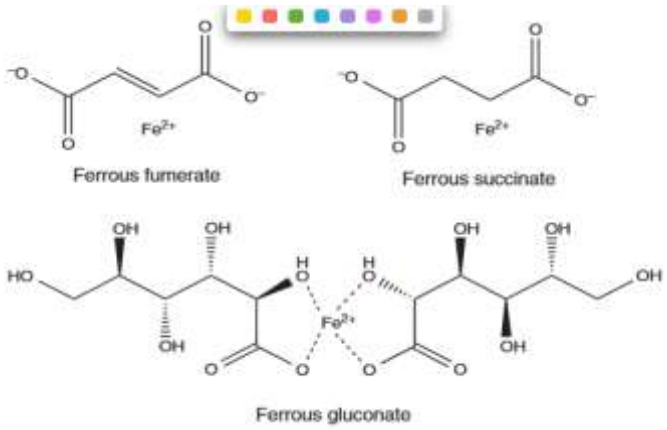
- A biophysicist Rosenberg, working at Michigan State University, discovered the anticancer activity of cisplatin in 1965.
- Rosenberg devised an experiment to investigate the effect of electric fields on cell division, in which he passed an alternating electric current through two Pt electrodes immersed in a beaker containing Escherichia coli bacteria in a cell growth medium containing ammonium and chloride ions.
- During the experiment, Rosenberg discovered that the bacteria had grown in size, but not divided as was expected. On carrying out some control experiments, it became soon clear that it was not the electric current that caused this unusual cell growth.
- Rosenberg realised that a chemical reaction had taken place in the cell medium requiring oxygen, ammonium ions (NH4+) and chloride ions (Cl−) in addition to a small amount of platinum, which was dissolved from the surface of the electrodes.
- A mixture of platinum salts was accidentally synthesised which contained cisplatin (cis-[Pt(II)$Cl_2(NH_3)_2$]). Rosenberg subsequently showed that only cis-[Pt(II)$Cl_2(NH_3)_2$] and not trans-[Pt(II)$Cl_2(NH_3)_2$] could prevent the growth of cancer cells in vitro. Typically, cisplatin kills cancer cells at micromolar doses.
- The anticancer activity of cisplatin is based on the interaction of the platinum complex with DNA located in the nucleus. Interaction with the mitochondrial DNA is believed to be less important for the antitumour activity of cisplatin. Cisplatin binds to DNA primarily by coordination to the nitrogen (N7) atom of guanine, whereas it also can bind to N7 and N1 of adenine and N3 of cytosine.

Medicinal use of Iron

- The lack of functional iron leads to anaemia, which is characterised by weakness in body. Usually, iron is administered orally as Fe2+ or Fe3+

salts. Fe2+ compounds are more soluble at physiological pH. The advantage of Fe3+ salts is that they are not prone to oxidation in aqueous solutions.

- The most common medicinal preparations include FeCl3, FeSO4, Fe(II) fumarate, Fe(II) succinate and Fe(II) gluconate. The oral dose of Fe2+ for the treatment of iron-deficiency anaemia is typically recommended as 100–200 mg/day. In the case of ferrous sulfate (FeSO4), this is equal to 65 mg of Fe2+, which is given three times per day.
- As a therapeutic response, the haemoglobin concentration should raise about 100–200 mg/100 ml/day. It is recommended continuing the treatment for 3 months once the normal range is reached.
- It is known that oral treatment with iron salts can lead to GI irritations. There is very little difference between the efficiency and absorbance rate of the above-mentioned iron salts.
- The choice of the preparation is influenced by side effects and cost. Iron salts such as iron dextran and iron sucrose can be administered by IV infusion or IV injection.



- This administration route should be chosen only when oral therapy is not successful, as there is a risk of anaphylactic reactions.

Radioactive compounds and their clinical applications

- Radiopharmaceuticals that are used therapeutically are molecules with radiolabelling. This means that certain atoms in this molecule have been exchanged by their radioactive isotopes.

- These radiolabelled molecules are designed to deliver therapeutic doses of ionising radiation (mostly β-radiation) to specific disease sites around the body. The more specific the targeting is, the fewer the side effects expected.

131-Iodine: therapy for hyperthyroidism

- Iodine has only one stable isotope (127I53), while 131I is the product of nuclear fission with β-emitting radioisotope and half lifetime of 8 days.
- When expose to nuclear radiation 131I can be transported to the thyroid gland if inhaled. Fortunately, it can be replaced by treatment with potassium iodide (nonradioactive), which will replace the radioisotope.
- 131I can be used as a therapeutic agent against thyroid cancer when applied in high doses. These prepared doses are normally administered orally either as capsules or solution.

89Strontium

- 89Sr is an artificial radioisotope with β-emitter and half-life of 50 days. It is a product of the neutron activation of 88Sr and decays to the stable 89yttrium.
- Metastron is a product containing 89Sr and is licensed by the FDA. It comes in a ready-to-use vial and expires within 28 days. It is supplied with a calibration vial, so that the pharmacist will be able to ensure that the patients get the accurate dose prescribed.
- Because of the similarity of strontium and calcium, strontium is believed to be metabolised in the human body in a similar way and accumulates, for example, in the bones. This has led to its application as a treatment option for pain caused by bone metastasis.
- It is known that >50% of patients with prostate, breast or lung cancer will develop painful bone metastasis. 89SrCl2 is administered intravenously and, as its distribution in the human body is like that of calcium, it is quickly cleared from the blood and deposited in the bone mineral.

- The radioisotope 89Sr delivers localised β-radiation, inducing a pain-relieving effect. A majority of the administered SrCl2 is actively distributed to the metastases. Any free SrCl2 is excreted renally or along with the faeces [2].

Boron neutron capture therapy (BNCT)

- Boron has two stable isotopes, 10B and 11B, and 14 radioisotopes with very short half-lives. 11B is the most abundant isotope and represents 80% of natural boron, whilst 10B (~20%) finds a significant clinical application in the so-called boron neutron capture therapy (BNCT).
- BNCT is a non-invasive treatment option for malignant tumours, especially brain tumours and head and neck cancers, and is currently under clinical trials.
- The patient is injected with a nonradioactive 10B-containing compound that acts as a neutron-capturing agent and shows high selectivity to cancer tissues.
- Once the compound has reached the tumour, the patient is exposed to a beam of low-energy neutrons. These neutrons lose their energy once they penetrate the skin, but they can still interact with the neutron-capturing agent and initiate a nuclear reaction. This reaction of 10B with a neutron result in the conversion to the nonradioactive isotope 7Li and low-energy gamma radiation together with the emission of α-radiation (42He2+ particles).

Q- Discuss the Detoxification and Chelating Agents in Medicine.

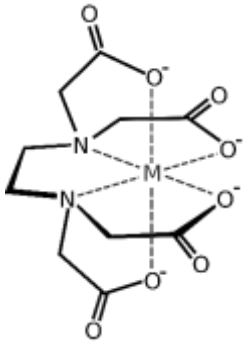
The treatment of **metal poisoning** or **detoxification** is done by the chelating agents because **chelating agent** will form **soluble**, **stable** and **non-toxic complexes** which will be readily excreted.

- There are some conditions for designing an effective chelating drug:
  1. It should **bind** the toxic metal such a way that it can **behave like biological ligands**.
  2. It should **not go** into **metabolic process**.

3. It should be **selective** for **toxic metal** which we want to remove from the body otherwise it will mobilize other essential metals out of the body.
4. It should have proper **availability** for **specific site** from where toxic metal has to be removed.
5. It should form **non-toxic complex** that should be **easily execrated** from the body.

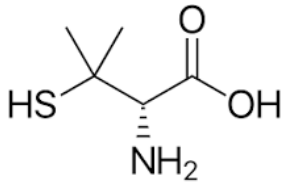
Examples:

1. EDTA (Ethylenediaminetetracetate):



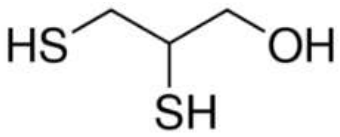
- Ni-EDTA complex was used for the treatment of cancer.
- [$CaNa_2EDTA$] is used for Pb poisoning.
- [Co_2EDTA] is used for CN poisoning.

2. D-Penicillamine:



- It is used to remove toxicity of Cu.

3. 2, 3-dimercapto-1-propanol (Bal):

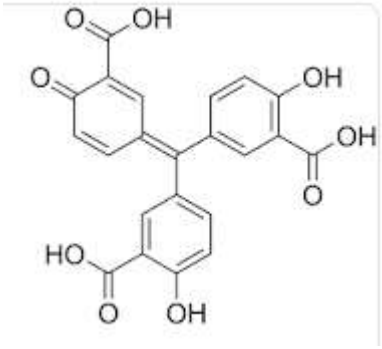


- It is known as British Anti-Lewisite (BAL) and used for treatment of poisoning caused by Hg, As, Gold etc. (Anti-Lewisite: Lewisite is a

type of chemical warfare agent. This kind of agent is called a vesicant or blistering agent, because it causes blistering of the skin and mucous membranes on contact. Lewisite is an oily, colourless liquid in its pure form and can appear amber to black in its impure form).

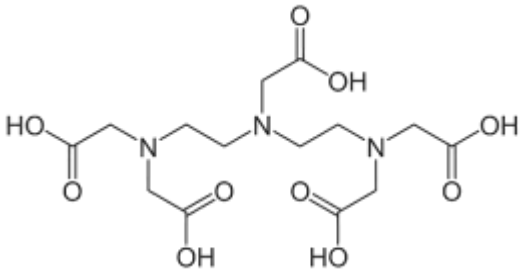
- First used during world war against lewisite gas to remove arsenic poisoning.

4. Aurintricarboxylic acid:



- Used for Be poisoning.

5. Diethylenetriamine pentaacetic acid (DTPA):



- It can bind with atoms of plutonium and other actinides to form a complex which can easily eliminate from the body.
- It can apply as salt of Ca and Zn.