Lecture No.1
Inorganic pharmaceutical chemistry

Reference:

Inorganic Medical and pharmaceutical Chemistry by Block Roche, Soine and Wilson.

Introduction

Pharmaceutical Chemistry is a branch of chemistry that deals with the chemical, biochemical and pharmacological aspects of drugs. It includes synthesis/isolation, identification, structural elucidation, structural modification, Structural Activity Relationship (SAR) studies, study of the chemical characteristics, biochemical changes after drug administration and their pharmacological effects.

Inorganic chemistry is the study of all the elements and their compounds except carbon and its compounds (which is studied under organic chemistry), it describes the characteristics of substances such as nonliving matter and minerals which are found in the earth except the class of organic compounds.

The term 'Pharmaceutical' is used for any chemical substance useful in preventive or therapeutic or which finds use in the preparation of medicament. Some find use only in the laboratory during the preparation but may not be present in the final product, these are also incorporated under pharmaceuticals. Quality of all these pharmaceuticals must be carefully controlled. For this reason, specifications of quality are mentioned for each pharmaceutical. These descriptions are reported in the pharmacopoeia.

Importance of Inorganic Pharmaceuticals

Inorganic pharmaceuticals are useful in any 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 alkalis. 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 aluminum hydride).
6. Useful in Pharmaceutical analysis. Example: Titrants such as potassium permanganate etc.

Classification Of Inorganic Pharmaceuticals

Inorganic Pharmaceuticals can be classified in two ways

1. Based on their uses.
2. Based on their application in therapy.

Classification based on their applications (therapeutic classification) is described below:

Acidosis: Acidosis is a pathologic condition resulting from accumulation of acid and hydrogen ions. Inorganic drugs used in this condition are all electrolyte replenishers like sodium chloride, potassium chloride and others.

Acne: Acne is a very common chronic inflammatory dermatosis in adolescent in both sexes. The lesions are seen on face, upper chest and upper back. Inorganic drugs used in this condition are sulphur and its compounds

Alkalosis: Alkalosis is a pathologic condition resulting from accumulation of base and characterized by decrease in hydrogen ion concentration. Inorganic drugs used in this condition are all acidic electrolyte replenishers like sodium chloride, potassium chloride.

Allergic diseases: Allergic disease is a state of hypersensitivity induced by exposure to a particular antigen (allergen) resulting from immunologic reaction. An inorganic drug used in this condition is magnesium thiosulphate.

Anaemia: is defined as decreased hemoglobin concentration in blood below the lower limit of the normal range of individual. Inorganic drugs used in this condition are, all iron compounds (Haematinics: Ferrous Sulphate, Ferrous gluconate, Ferric ammonium citrate etc.).

Anoxia: It is a condition characterized by an absence of oxygen supply to an organ or a tissue. Oxygen is used in this condition.

Arthritis: It is a chronic systemic disease manifested as inflammation of peripheral joints and hematological, pulmonary, cardiovascular and neurological abnormalities. Inorganic drug used in this condition is sodium aurothiomalate.

Asphyxia: A condition in which extreme decrease in the concentration of oxygen in the body accompanied with increase in the concentration of carbon dioxide level leads to unconscious or death. Oxygen is used in this condition.

Asthma: Asthma is characterized by hyper responsiveness of bronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes accompanied by increased secretions; symptoms include wheezing, cough, and dyspnoea. Organic drugs like salbutamol are used in this condition.

Athlete's foot (Tinea pedis): It is a superficial fungal infection of stratum corneum of skin, located in the web spaces between toes. Inorganic drugs used in this condition are sodium pyrophosphate.

Boils: Bacterial infection of hair follicles and surroundings. An inorganic drug used in this condition is magnesium sulphate.

Burns: Injuries to the tissues caused by frictions, heat, radiation, electricity or chemicals. Inorganic drugs used in this condition are silver nitrate, oxygen, zinc peroxide.

Carbuncles: Carbuncle is a bacterial infection spread under the skin and subcutaneous tissue with oozing of pus. Inorganic drug used in this condition is magnesium sulphate.

Various uses of inorganic pharmaceuticals in pharmacy are presented here in

Abrasives: Drugs which are used for the cleaning and whitening of teeth. Example: Dibasic calcium phosphate.

Absorbents: Drugs which are used to absorb the toxins and bacteria in the GIT. Example: Calcium carbonate.

Acidifiers: Drugs which are used to enhance the acidity temporarily in GIT. Example: Dilute hydrochloric acid.

Adsorbents: Drugs which are used in the treatment of mild dysentery or diarrhea or other disturbances of GIT due to their ability to adsorb gases, toxins, and bacteria. Example: Bismuth sub-carbonate, Bismuth subnitrate.

Alkalizers: Drugs which are used to induce the alkaline condition or used in acidic condition of body. Example: Sodium citrate.

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

Analgesic: Drugs which are used to relieve pain. Example: Nitrous oxide.

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

Anthelmintics: Compounds used for the treatment of worm infestations or schistosomiasis. Example: Ammoniated mercury, Sodium antimony tartrate.

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

Anticonvulsants: Drugs which are used for the treatment of epilepsy. Example: Potassium bromide.

Anti coagulants: Drugs which are used to prevent blood clotting. Example: Sodium citrate.

Anti-depressants: Drugs which are used in the treatment of depression. Example: Lithium carbonate.

Antidotes: Drugs which are used in the treatment of poison. Example: Sodium nitrite, Sodium thiosulphate.

Antifebriles: Drugs which are used to relieve pain or reduce fever. Example: Ammonium acetate.

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

Anti-hypercalcemic agents: Drugs which are used in the treatment of abnormal calcium concentration in the body. Example: Sodium acid phosphate.

Anti-infectives: Drugs which are used in the treatment of local infections. Example: Potassium permanganate; Silver nitrate, Hydrogen peroxide, Boric acid.

Anti-inflammatory agents: Drugs which are used in the treatment of inflammatory pain (Rheumatoid arthritis). Example: Sodium aurothiomalate.

Anti irritant agents: Drugs which are used to prevent irritation or allergic reactions. Example: Aluminum metal powder.
Antiseptics: Drugs which are used to inhibit the growth and development of microorganism without killing. Example: Strong iodine solution.
Antiperspirants: Drugs which are used to remove the bad odour in body. Example: Aluminum sulphate.
Anti-protozoal: Drugs which are used in the treatment of protozoal infections or Leishmaniasis. Example: Sodium antimony gluconate.
Anti pruritic (topical): Drugs which are used in the production of soothing effect in the skin. Example: Calamine.
Anti rheumatics: Drugs which are used in the treatment of rheumatism. Example**:** Sodium aurothiomalate.
Anti thyroids: Drugs which are used in the treatment of thyrotoxicosis. Example**:** Potassium perchlorate.
Anti-tumor agents: Drugs which are used in the treatment of cancer. Example: Cisplatin (Testicular and ovarian cancer).
Anti-schistosomal agents: Drugs which are used in the treatment of schistosomiasis. Example: Sodium antimony tartrate.
Antioxidants: Substances that prevents or delays oxidation. Some formulations, vegetable oils and prepared foods contain antioxidants. Example: Sodium bisulphate, sodium metabisulphite, sodium sulphite.
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, Aluminum citrate.
Bactericides: Drugs which are used to kill bacteria. Example: Potassium permanganate.
Bacteriostatics: Drugs which are used to prevent the growth of bacteria. Example: Alum, borax (local bacteriostatic).
Bleaching agents: Drugs which are used in the cleansing of wounds or bleaching. Example: Hydrogen peroxide.
Buffers: Substance which prevents the change in pH upon addition of acid or base. Example: Acetate buffer (pH – 3.9), Sodium citrate buffer.
Calcium supplements: Drugs which are used as a calcium source. Example: Calcium lactate, Calcium gluconate.
Cathartics: Drugs which are used to enhance defecation, removes constipation and expulsion of intestinal parasites. Example: Calomel, Magnesium sulphate.
Chlorine source: Substance which liberates chlorine. Example: Chlorinated lime, Chlorinated soda.
Dentifrices: Drugs which are used in cleaning the surface of the teeth. Example: Calcium carbonate, Magnesium peroxide.

Depilatory agents: Drugs which are used to remove hair. Example: Barium sulphide.
Diagnostic agents: Drugs which are used in diagnose the diseased conditions of the organs. Example: Barium sulphate.
Diaphoretics: Drugs which are used to promote sweating. Example: Potassium citrate.
Disinfectants: Drugs which are used to kill the microbes in nonliving things. Example: Ammonium acetate.
Diuretics: Drugs which are used to increase the urine output. Example: Ammonium chloride, Ammonium iodide.
Dressing material: Substances which are used for the dressing of burns. Example: Aluminum metal foil.
Dusting powders: Substance which are used to have soothing effect on the skin. Example: Talc, Zinc stearate, Light kaolin.
Electrolyte replenishers: Compounds used to treat acid base imbalance conditions in the body. Example: Sodium chloride, Ringer lactate solution, Potassium chloride.
Emetics: Drugs which are used to induce vomiting. Example: Zinc sulphate, Copper sulphate.
Expectorants: Drugs which are used in the treatment of cough. They promote the ejection of mucus (sputum) from the lungs, bronchi and trachea by increasing its fluidity (reducing viscosity). Example: Potassium iodide (sedative expectorant), Eucalyptus, Lemon (stimulant expectorant), Ammonium chloride, Potassium iodide.
Fillers: Drugs which are used to fill the dental cavities. Example: Gold and Silver metals.
General an aesthetics: Drugs which are used to produce reversible loss of sensation**.** Example: Nitrous oxide.
Germicides: Drugs which are used to kill the germs. Example: Chlorinated lime.
Haematinics: Drugs which are used in the treatment of anemia. Example: Ferrous sulphate, Ferric ammonium citrate and other iron compounds.
Haemostatic: Drugs which are used to arrest the flow of blood. Example: Alum.
Inhalants: Inhalants are the drugs or chemicals which in the vapor form are inhaled or administered through the respiratory system in the body. Example: Oxygen, CO_2, Ammonium carbonate, Nitrous oxide, Helium.
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.
Protectives: Substance which tend to form a coating and protect the exposed skin or mucus membrane from harmful stimuli. Example: Zinc stearate, Zinc oxide.
Purgatives: Drugs which are used to defecate. These agents relieve constipation and helps in the expulsion of intestinal parasites. Example: Magnesium sulphate.

Radiation shields: Compounds which are used to prevent the entry of radiations. Example: Lead sheets, Wall lining.
Radio isotope tracers: Radioactive element or compound added to material to monitor the material's distribution as it progresses through a system. Example: Carbon-14, Tritium.
Radiotherapeutic agents: Radioisotopes used for the treatment of diseases. Example: Iodine-121, Cr- 52 and Gold- 198.
Rubefacients: Substances which causes reddening of skin by dilating blood vessels and increasing blood circulation in the applied area. Example: Ammonia.
Scabicides: Drugs which are used in the treatment of scabies. Example: Sulphur.
Sedatives: Substance which causes CNS depression and produces sedation. At higher dose they produce sleep. Example: Potassium bromide, Lithium carbonate

Importance of inorganic compounds in pharmacy and medicine
Sources of impurities, an outline of methods of preparation, heavy metals, uses, tests for purity and identity, sulphate and special tests, inorganic pharmaceuticals included in Iraqi Pharmacopoeia, including limit tests for iron, arsenic, lead, chloride
Gastrointestinal Agents: Protectives and Adsorbents, Acidifying agents, Antacids, Cathartics, Major Intra- and Extra-cellular.
Electrolytes: Electrolytes used for replacement therapy, Physiological ions, acid-base balance and combination therapy.
Essential and Trace Elements: Transition elements and their compounds of pharmaceutical importance, Cationic and anionic components of inorganic drugs useful for systemic effects, Iron and haematinics, mineral supplements
Topical Agents: Protective's, Astringents and Anti-invectives
Gases and Vapors: Oxygen, Anesthetics (inorganic) and Respiratory stimulants
Dental Products: Dentifrices, Complexing and chelating agents used in therapy, Anti-caries agents
Miscellaneous Agents: Emetics, Sclerosing agents, Inorganic poisons and antidotes, Expectorants
Pharmaceutical Aids Used in Pharmaceutical Industry: Filter aids, Anti-oxidants, Adsorbents, Suspending agents, Preservatives, Colorants, Diluents, Excipients.
Acids, Bases and Buffers: Calculations and methods of adjusting isotonicity, Buffer equations and buffer capacity in general, buffers in pharmaceutical systems, stability, buffered isotonic solutions, preparation, measurements of tonicity
Inorganic Radiopharmaceuticals: Nuclear reaction, dosage, Methods of obtaining their standards and units of activity, radioisotopes, hazards and precautions, half-life, radiopharmaceuticals, clinical applications, Nomenclature, measurement of activity.

Electronic Structure of Atoms
Subatomic Particles and their properties

Atomic Orbitals 1s 2s2p 3s3p……..

- Quantum numbers (n, l, m_l, m_s)

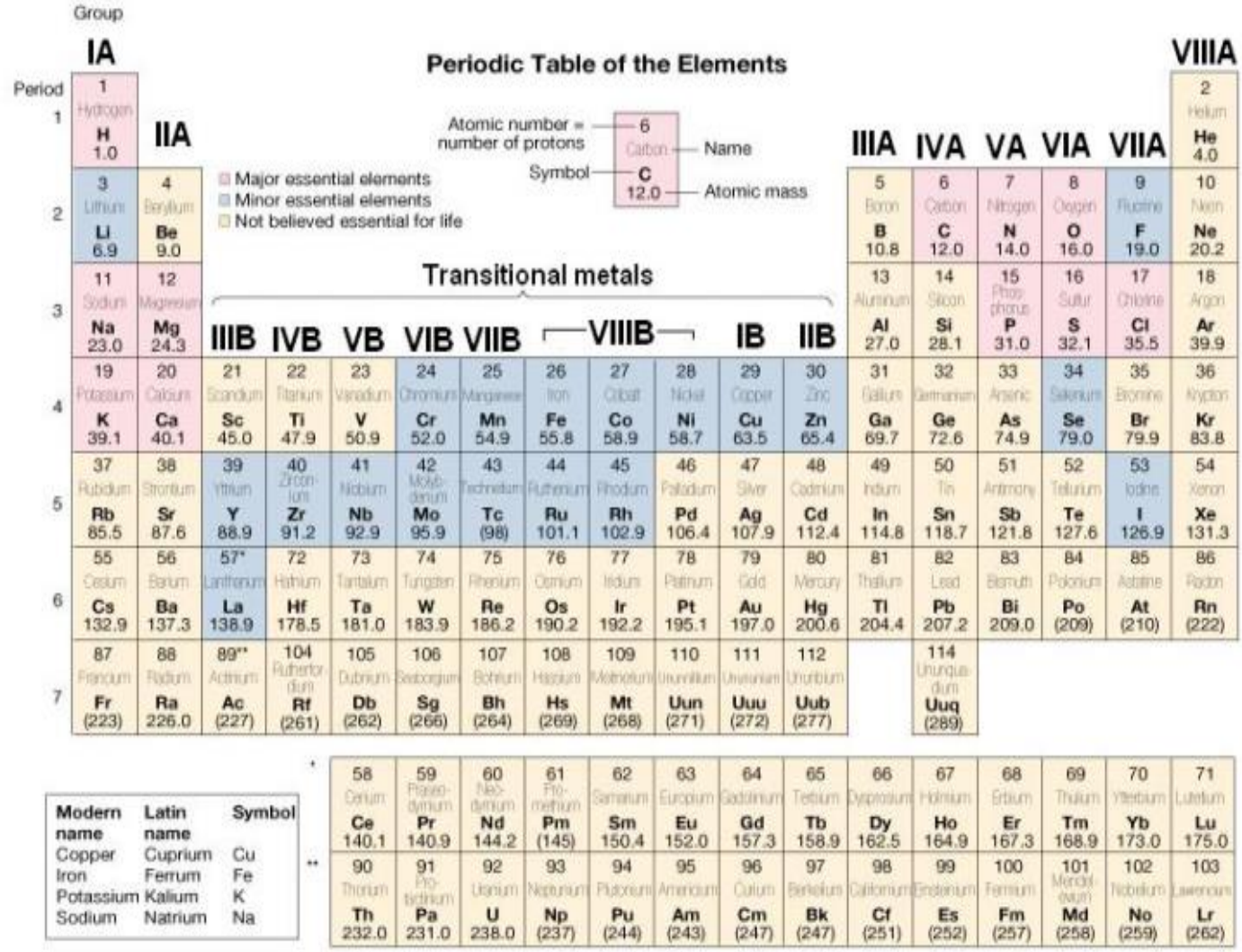
- Representation of Atomic Orbitals

- Atomic Orbital filling applying Hund's rule and stability considerations

e.g. Cr and Cu with z= 24 and 29 respectively

The Periodic Law

Electronegativity, definition and order



Electronic Structure of Molecules; δ, л, n, л*, δ*

Coulombic attraction, electron –electron Repulsion and nuclear repulsion

Covalent; sharing of electron pairs

Ionic; electrostatic interaction

Orbital Hybridization- It involves mixing of atomic orbitals to provide a new set of degenerate orbitals having different spatial orientations and directional properties than the original atomic orbitals. Examples using Be, B and C including shapes and properties.
sp, sp^2, sp^3, d^2sp^3. The effect of ligand strength and the magnetic properties of the complex in determining shape e.g. octahedral, tetrahedral or square planar.

Types of Bonding Interactions

Ionic Bonding, e.g. sodium and calcium chlorides

Covalent Bonding, e.g. hydrogen, chlorine, carbon, hydrocarbons, phosphorus, carbon dioxide and hydrogen cyanide.

Coordinate Covalent Bonding, e.g. in boron-trifluride etherate.

Q: What determines the nature of a bond?

Hydrogen Bonding

Hydrogen bonding is a weak secondary interaction usually intramolecular and also intermolecular. It explains some of the unusual properties of water such as its relatively high boiling point. It is also important in describing the structures of proteins and nucleic acids. To form a H-bond, there must exist a hydrogen atom attached directly to one of the three atoms F, O or Nitrogen. These atoms have high electronegativities.

Van der Waals Forces

Van der Waals forces are weak intermolecular forces to explain important phenomena including halogens and hydrocarbons as well as drug – receptor. These interactions depend on masses and distance between molecules.

Other types of Interactions

Polar interactions as well as induced dipole interactions are week forces.

However, they are important in explaining some properties of compounds as well as drug – receptor interactions and the relative stability of some isomers. Apart of the extreme cases of pure covalent bonding of homonuclear diatomic molecules and pure ionic bonding between GI and GVII atoms, these is always varying degrees of ionic or covalent character described in terms of polarity. The later depends on;

1. polarisabilty, highest for cations of high q/r
2. polarising power, highest for anions of high q/r
3. dipole moment, difference in electronegativities.

Polarisation

Apart of the extreme cases of pure covalent bonding of homonuclear diatomic molecules and pure ionic bonding between GI and GVII atoms, these is always varying degrees of ionic or covalent character described in terms of polarity. The later depends on;

Coordination Compounds

Metallic cations, especially the transition metals are able to form stable compounds with additional anions or molecules with lone pair(s) of electrons, ligands, to form complexes. The

maximum number of sites of the central metaloccupied is called the coordination number.The metal and its associated ligands is called the complex ion. The later with its counter ions is called the coordination compound. The stability of a complex depends on the metal ion and the basicity of the ligand, Lewis's concept. Ligands can be bidentate, tridentate, tertradentate, hexadentate or octadenate

Bonding in Complexes

The valence bond theory is used to obtain a quantitative picture of bonding in complexes. The theory uses the idea of hybridization of the central metal atomic orbitals. The orientation of the five d orbitals of the metal in a complex is made of two sets. The d_{x2-y2} and d_{z2} orbitals are oriented along the axes of the Cartesian coordinate system. The other three; d_{xy}, d_{yz} and d_{xz} are directed between the axes.

Octahedral Complexes, 1-3 electrons

For transition metals containing 1-3 electron in the d orbital e.g Cr+3 complexing with six cyano, CN^- ions to form $[Cr(CN)_6]^{-3}$. Chromium (III) is a d^3 ion; that is, it contains 3e in the in its 3d valance orbital. These electrons are unpaired and occupy the three off-axis d orbitals, thus leaving two d, one s and 3p orbitals empty for bonding with six cyano groups. If these six orbitals hybridize six equivalent orbitals are formed and will be occupied by the six lone pairs of electrons donated by the six cyano ligands.

Octahedral Complexes, 4-6 electrons

When four or more electrons in the outer d orbital, for example complexes formed with iron (III) which is a d5 ion, the normal ground state arrangement of electrons use different orbitals for bonding. In hexaaquoiron (III) which is a high spin complex, with similar magnetic moment as the free ion, hybridization of six orbitals (five 4d, one 4s, and three 4p) called outer orbital hybridization, sp3d2 instead of the usual sp3d2 hybridization. If the water molecules in hexaaquoiron(III) complex ion are replaced with cyano groups, the hexacyanoferrate (III) ion results which has lower magnetic moment, a low spin complex. This is a result of the high magnetic field of the cyano groups of sufficient strength to repel the electrons in the two d orbitals which directly oppose the approaching ligands. The electrons become paired with those in the other d orbitals. Pairing with the six orbitals of the ligands will result in a low spin octahedral complex.

Complexes with 7-9 d electrons

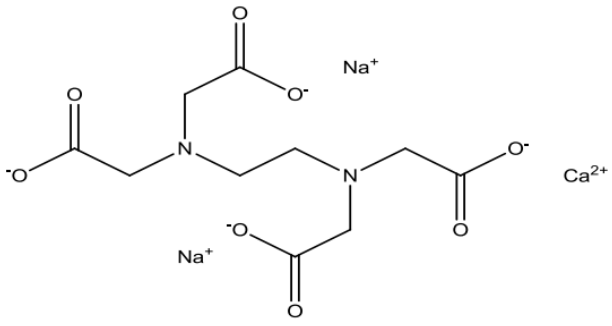
Transition metal ions with seven, eight, or nine d electrons generally have coordination number of 4 which leads to either a square planar or a tetrahedral arrangement of the ligands.

The strength of the ligand and the formation of high – and low spin complexes may be predicative of the type of hybridization and therefore the geometry of the complex. For example a d8 ion complexing with a ligand having a relatively weak electrostatic field has no d orbitals available for bonding. However, the ligands can bond through the four sp3 hybrid orbitals formed on the metal to give a tetrahedral complex. A strong ligand will force the

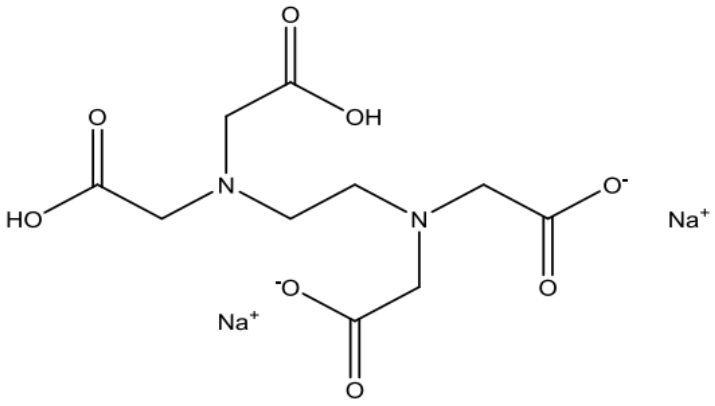
metal into a low spin state and a square planar resulting from dsp3 hybridization will be formed. The complex has one vacant d orbital.

Complexes and Chelating Agents

Chelating agents are important aspects of pharmacy, drug therapy. They have much efficacy in the treatment of heavy metal poisoning for elements such as leas, arsenic, mercury and iron. Chelating agents are important in treatment of metabolic disorders where metals such as iron and copper are accumulated in abnormal amounts in various tissues. Examples of important chelating agents include EDTA, BAL, penicillamine and deferoxamine.



calcium disodium edetate

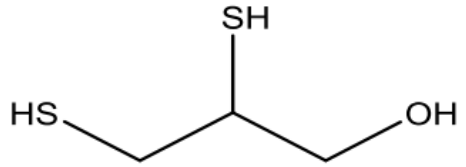


disodium edetate

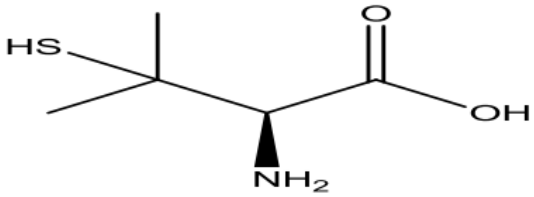
Disodium salt of EDTA is a mixture of the dihydrate salt. It is a white crystalline granules or powder. It is odorless, slightly hygroscopic and has a faint saline taste. It is stable in air, soluble in water with pH between 6.5 and 8.0. It is used in the treatment of heavy metal poisoning especially plumbsim and other metals but not for mercury arsenic or gold. An increase in the excretion of metal in the urine by 500ug/liter/24hr is an indication of poisoning. It induces hypocalcaemia states. Doses are IV or IM of 75mg/kg of body weight.

Preparation; a solution containing 200mg/ml for injection. Disodium edetate is a white crystalline powder which is soluble in water and has pH of 4.0-6.0. It is used in treatment related to hypercalcemia including occlusive vascular disease and cardiac arrhythmias. It is

not useful for dissolution of urinary calculi. Doses; IV injections of 50mg/kg of body weight. Preparation; 150mg/ml for injection.



2,3-bis(sulfanyl)propan-1-ol



penicillamine

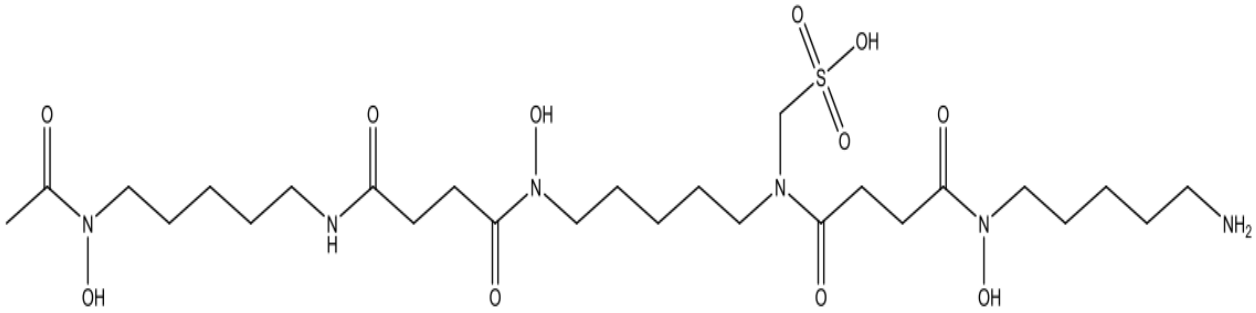
Dimercaprol (PAL) is a colorless of mercaptan-like odor. It competes with enzymes containing sulfhydryl groups (responsible for oxidation-reduction) for the metals causing poisoning. The mercaptides formed are excreted in the urine. BAL is of value in the treatment of arsenic or gold poisoning and early mercury poisoning, within a few hours.

Dose: in severe arsenic or gold poisoning, 3.0mg/kg is given six times a day for two days, four times a day on the third day, then twice daily on the next ten days. For early mercury poisoning, 5.0mg/kg followed by 2.5mg/kg twice daily for ten days. Preparations: IM imgectio of 100mg/ml in peanut oil.

Pencillamine is a white crystalline powder having characteristic odor. It is freely soluble in water with pH of 4.5-5.5. Pencillamine is used for treatment of poisoning of many metal including lead, iron, mercury and gold. Pencillamine is used for treatment of hepatolentecular degeneration (degeneration of the brain associated with increased levels of copper and Wilson's disease which is associated with elevated levels of copper in tissues including; eye, liver, brain and kidney. Pencillamine is used in the treatment of gold dermatitis. Pencillamine is used in the treatment of cystinurea, the presence of crystals of
cystine in urea.

Dose: 250mg capsules given four times a day. Preparations: Cuprimine capsules containing 250mg of penicillaime for oral administration. The effectiveness of pencillamine as compared to is attributed ;

1. its ability to resist metabolic inactivation by aa oxidase since it doesn't have a hydrogen on the beta carbon atom.
2. its sulfhydryl group ability to convert Cu+2 to Cu+, with the formation of a tetrahedral rather than a square planar complex which has less affinity in competition with the tissue proteins containing –SH groups of oxidative value.



N-[5-[[4-[5-[acetyl(hydroxy)amino]pentylamino]-4-oxobutanoyl]-hydroxyamino]pentyl]-N'-(5-aminopentyl)-N'-hydroxybutanediamide;methanesulfonic acid

Deferoxamine is for acute iron deficiency. It forms an octahedral complex with Fe+3. It has no affinity to divalent ions including Fe+2. Deferoxamine is not soluble in the gastrointestinal tract so oral administration is not effective. It is produced by streptomyces as as a ferric Fe(III)complex. After chemical removal of the iron, the chelating agent is purified as the methyl sulphonate salt. Dose: IV or IM injections of 1.0g followed by 0.5g every 4-12 hours. Preparations: Desferal ampules containing 500mg of the lyophilized powder for injection.