Branch: B. Pharm.
Semester: I
Subject: Pharmaceutical Inorganic Chemistry
Subject code:BP104T
UNIT-IV
Topic: Miscellaneous compounds

Dr. LUBNA AZMI
Assistant Professor
Department of Pharmaceutical Chemistry
Institute of Pharmaceutical Sciences
University of Lucknow

EXPECTORANTS

❖The cough is a protective physiological reflux (both, voluntary and involuntary) to clear the airway.

❖Infections, chemical irritants, retained body secretions and the presence of foreign bodies that block one's airways and causes coughing by stimulating the nerve endings in the respiratory tract.

❖**Dry and Productive Cough:** Irritative or unproductive cough is dry cough, which may be caused by colds or by inhalation of irritating dust and gases and produces no sputum or other discharge,

❖ whereas productive cough is sputum or exudate producing cough and is often associated with asthma and bronchitis.

❖**Expectorants** are drugs used to help in the removal (expulsion) of secretions or exudate from the trachea, bronchi, or lungs, and hence they are used in the treatment of cough.

❖They act upon the respiratory tract in two ways

- ❖ **By decreasing the viscosity of the bronchial secretion and facilitating their elimination; local irritants are expelled and ineffectual coughing is alleviated; and**
- ❖ **By increasing the amount of respiratory tract fluid, a demulcent action is exerted on dry mucosal linings, thus relieving the unproductive cough. It is believed that many of them act by reflux by irritating the gastric mucosa which, in turn, stimulates respiratory tract secretions.**

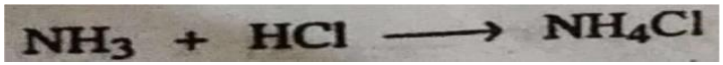
Examples: Inorganic saline expectorants are ammonium salts (**ammonium chloride**), iodides (**potassium iodide**/sodium iodides), citrates and antimony potassium tartrate.

Sometimes, emetics in low doses are used in cough preparations. They probably stimulate flow of respiratory secretions. *The rationale of adding an emetic in the cough syrup containing opiate (addicting and antitussive (cough-suppressant)) is, that, the patient would become nauseated if an excessive dose is consumed.*

AMMONIUM CHLORIDE

NH_4Cl

Ammonium chloride is prepared by neutralizing hydrochloric acid with ammonia.



❖The resulting solution of ammonium chloride is evaporated to dryness. The crude product thus formed is purified either by recrystallization or by sublimation.

❖**Properties:** Ammonium chloride occurs as colourless crystals or as white crystalline powder. It is somewhat hygroscopic. It is odourless and possesses cooling saline taste. It is freely soluble in water but sparingly; soluble in alcohol.

❖Its 5% solution is acidic (pH 4.5 to pH 6.0). On heating it sublimes without melting.

❖**Uses**

(l) Expectorant: Ammonium Chloride in doses of 300 mg to 1 gm is used as an ingredient in expectorant cough mixtures.

❖**Diuretic: It is given for its diuretic action especially to help the excretion of over dosage of basic drugs such as amphetamine and in the treatment of lead poisoning, by increasing its excretion.**

❖**Systemic acidifier:** It is helpful in producing mild acidosis. For this purpose, it is given by mouth in a dose of 2 g. It is rapidly absorbed through

❖G.I.T. and is converted into urea in the liver.

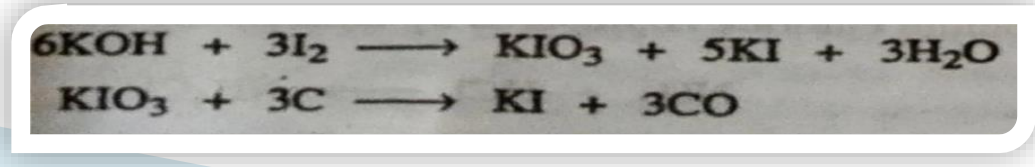
❖Thus, the anion liberated into the blood stream and extracellular fluids, causes a metabolic acidosis and decreases the pH of the urine (this is followed by transient diuresis).

❖It is also used to increase the diuretic effect of mercurial diuretics or to correct hypochloraemia alkalosis caused by prolonged use of mercurial and in the treatment of urinary infections when a low pH is required.

POTASSIUM IODIDE KI

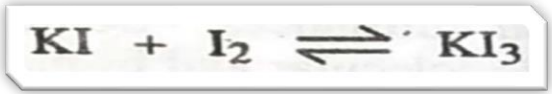
❖**Preparation:** It is prepared by treating slight excess of iodine with a hot aqueous solution of potassium hydroxide. The pale yellow solution is evaporated to dryness and residue is heated with charcoal to reduce the iodate.

❖*The product is extracted with water and filtered and the filtrate is evaporated to crystallization.*



Properties:

1. It occurs as cubic or hexahedral crystals either transparent and colourless, or somewhat opaque and white or as a white granular powder.
2. It is slightly hygroscopic
3. Its solution is neutral or slightly alkaline to litmus. It is very soluble in water and even more so in boiling water, freely soluble in glycerin and soluble in alcohol
4. On long exposure to air it becomes yellow due to liberation of iodine
   and small quantity of iodate may be formed. Light and moisture accelerate the decomposition.
5. Iodine readily dissolves in an aqueous solution of potassium iodide, forming a dark brown solution containing potassium triiodide.



Uses

1. Expectorant: It is used as an ingredient of expectorant mixture. The usual expectorant dose is 300 mg four times a day with dosage range of 300 mg to 2 g daily.
2. Source of iodine: It may be used for the prophylaxis and treatment of simple goitre
3. Antifungal: It is used as antifungal agent in veterinary practice.
4. Iodine solutions. It is one of the most important ingredient of various official iodine solutions (Antimicrobials).

Emetics

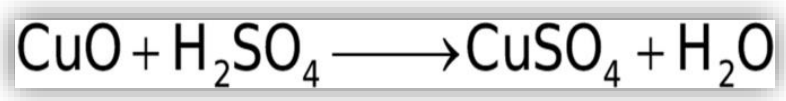
❖An emetic is a drug which induces vomiting. Emetics act either directly by stimulation of the chemoreceptor trigger zone, located in the area of postrema of medulla oblongata; or by reflux action of irritant on gastrointestinal tract.

❖Examples: Inorganic compounds e.g. copper Sulphate, sodium chloride, Zinc sulphate and antimony potassium tartrate show emetic effect. The clinical value of emetics, these days, has been lessened by the ***stomach tube***- a safer and more effective tool for emptying the stomach.

❖***Emetics are contraindicated in debilitated patients and in poisoning caused by corrosive or petroleum products.***

Copper Sulphate

$CuSO_4.5H_2O$



$$CuO + H_2SO_4 \longrightarrow CuSO_4 + H_2O$$

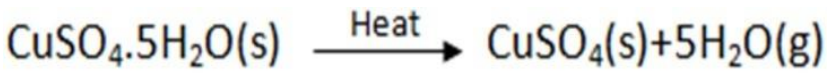
$$Cu(OH)2 + H2SO4 \rightarrow CuSO4 + 12H2O$$

Properties

It is a greenish-grey powder (Anhydrous) and blue (pentahydrate), very hygroscopic, freely soluble in water, slightly soluble in methanol, practically insoluble in alcohol.

Chemical Properties

Copper sulphate pentahydrate contain 5 moles of water per one mole of copper (II) sulphate. Its formula is written as $CuSO4.5H2O$. It can be converted into anhydrous copper sulphate when heated strongly. The blue colour of copper sulphate is due to water of hydration. When heated, it loses two water molecules at ~63°C followed by two more at ~109°C and the final water molecule at ~200°C and turns to white coloured anhydrous copper sulphate.



$$CuSO_4.5H_2O(s) \xrightarrow{Heat} CuSO_4(s) + 5H_2O(g)$$

The above process can be reversed, when water is added to white coloured anhydrous copper sulphate, its colour changes to blue, indicating that the

blue coloured copper sulphate pentahydrate is regenerated. So, it is a reversible chemical change.

On further heating at ~650°C, the anhydrous copper sulphate decomposes to form copper oxide (CuO) and sulphur trioxide and the reaction become irreversible.

Uses: Used as an Emetic (but not a drug of choice)

Hematinics

❖The recommended dietary allowances per day are **10 mg in male and 18 mg in female.**

❖ During **growth, menstruation, pregnancy** and pathological bleeding demand of iron increases considerably.

❖ It is absorbed according to the body requirements and the absorption increases in presence of **HCl and ascorbic acid (vitamin C).**

❖Apart from haemoglobin, it is also associated **with myoglobin, catalase, ferredoxin, cytochromes, electron transport and enzyme cofactor.**

❖ The deficiency of iron in the body is clinically manifested by anaemia (**hypochromic i.e. lack of haemoglobin in the blood)** and the excess of iron results in haemochromatosis.

❖Internal iron preparations are used to supplement the iron present in the body which is so essential in the formation of haemoglobin and various **physiological necessities mentioned in the previous paragraph**

❖Currently, **the IP 1996** includes Ferrous Fumarate, Ferrous Gluconate, Ferrous Sulphate including Dried Ferrous Sulphate, and Iron Ammonium Citrate as oral official substances in the monograph and other includes sodium iron edetate, iron dextran injection and iron sorbitol injection.

FERROUS SULPHATE

$FeSO_4.7H_2O$

Preparation

It is prepared by adding a slight excess of iron to dilute sulphuric acid. The crystals ($FeSO_4.7H_2O$) are separated and dried at room temperature.

$$Fe + H_2SO_4 \rightarrow FeSO_4 + H_2$$

Slight excess of iron is used so that all the sulphuric acid is fully consumed and no free sulphuric acid goes to the filtrate.

Properties

❖It occurs as transparent green crystals or as pale bluish green crystalline powder.

❖**It is odourless** and its taste is metallic and astringent. It is freely soluble in water but is insoluble in alcohol.

❖Ferrous sulphate loses 6 molecules of water of crystallisation at **38 ^{0}C**; and at higher temperatures basic sulphate are produced.

❖When exposed to moist air it is oxidised and becomes brown in colour.

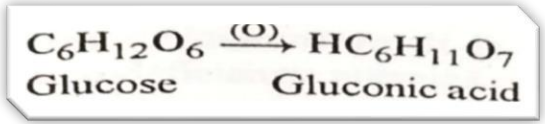
Uses:

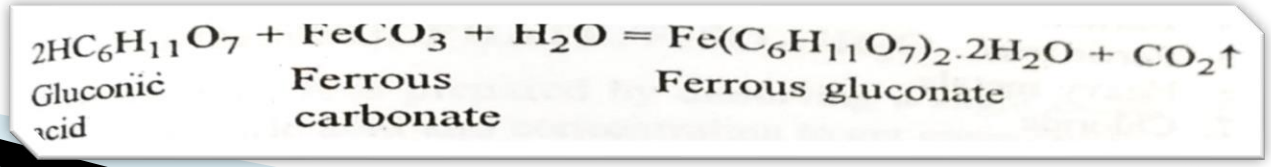
1. It is used as a haematinic i.e. it is used in the treatment of anaemia caused by iron deficiency.
2. It is used to dye fabrics and in tanning leather. It is also used in the manufacture of ink and in photography.
3. It possesses disinfectant property.

Ferrous Gluconate

$[CH_2OH(CHOH)_4COO]_2Fe.2H_2O$

Glucose is oxidised by bacterial fermentation to gluconic acid. The gluconic acid so obtained is treated with ferrous carbonate to give ferrous gluconate. It is crystallized with 2 molecules of water of hydration and dried.





Physical and Chemical Properties

Ferrous gluconate occurs as yellowish-grey or pale greenish yellow fine powder or granules. It has a slight odour like that of burnt sugar. It is fairly soluble in cold water and more soluble in warm water.

Medicinal Uses:

Haematinics: It is used in the prevention and treatment of iron-deficiency anaemias.

Poison and Antidote

Cyanide poisoning

❖Exposure to a high dose of cyanide **(inhalation of hydrocyanic acid or cyanamide, cyanogen chloride and silver polishes)** can result in death within minutes due to the inhibition of cytochrome oxidase (by binding with Fe^{3+} of cytochrome) resulting in arrest of cellular respiration.

❖Specifically, cyanide binds rapidly with **cytochrome a3,** a component of the cytochrome c oxidase complex in mitochondria. Inhibition of cytochrome a3 prevents the cell from using oxygen and forces anaerobic metabolism, resulting in lactate production, cellular hypoxia and metabolic acidosis.

❖In massive acute cyanide poisoning, the mechanism of toxicity may involve other enzyme systems as well.

Mechanism of action (Sodium Nitrite and Sodium thiosulphate as an Antidote)

The synergy resulting from treatment of cyanide poisoning with the combination of sodium nitrite and sodium thiosulfate is the result of differences in their primary mechanisms of action as antidotes for cyanide poisoning.

❖**Sodium nitrite** is thought to exert its therapeutic effect by reacting with hemoglobin to **form methemoglobin,**

❖an oxidized form of hemoglobin incapable of oxygen transport but with high affinity for cyanide.

❖Cyanide preferentially binds to methemoglobin over cytochrome a3, forming the nontoxic cyanomethemoglobin.

❖ Methemoglobin displaces cyanide from **cytochrome oxidase, allowing resumption of aerobic metabolism.** The chemical reaction is as follows:

$NaNO_2$ + Hemoglobin → Methemoglobin HCN + Methemoglobin → Cyanomethemoglobin

Vasodilation has also been reported as the side effect of sodium nitrite.

After administration of sodium nitrite (injection) **sodium thiosulphate** is injected to convert the cyanide further to thiocyanate which is also not toxic, thus increasing the activity of **endogenous detoxification.**

$$Na_2S_2O_3 + CN \rightarrow SCN^- + Na_2S_2O_3$$

Endogenous detoxification

Rhodanese, also known as rhodanase/thiosulfate thiotransferase, is a mitochondrial enzyme that detoxifies cyanide (CN^-) by converting it to thiocyanate (SCN^-).

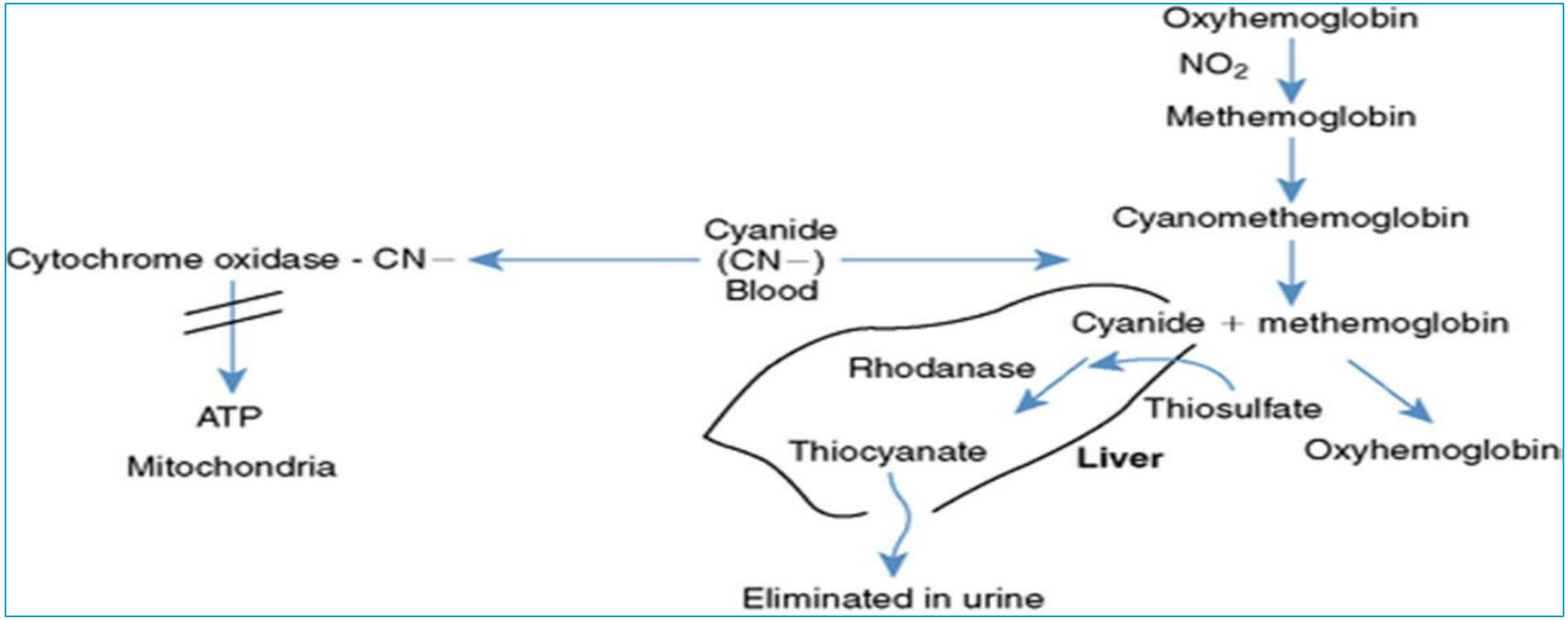


Figure: Cyanide poisoning and treatment with Sodium nitrite and Sodium thiosulphate

Usual dose as Antidote in Cyanide Poisoning

Sodium Nitrite: 10 to 15 ml of 3% solution intravenously.
Sodium thiosulphate: 1g (range 500 mg to 2g) in 5 to 10% solution intravenously

Sodium thiosulfate (sodium thiosulphate)

$Na_2S_2O_3 \cdot 5H_2O$

Typically it is available as the white or colourless. The solid is an efflorescent (loses water readily) crystalline substance that dissolves well in water.

Preparation

1. In the laboratory, this salt can be prepared by heating an aqueous solution of sodium sulphite with sulphur or by boiling aqueous sodium hydroxide and sulphur.

$$6\ NaOH + 4\ S \rightarrow 2\ Na_2S + Na_2S_2O_3 + 3H_2O$$

Chemical Properties

1. Under normal conditions, acidification of solutions of sodium thiosulphate excess with even dilute acids results in complete decomposition to sulphur, sulphur dioxide, and water.

2. Upon heating to 300 °C, it decomposes to sodium sulphate and sodium polysulfide:

Uses

1. Used as antioxidants with KI solution
2. Used as topical antifungal agent.
3. Used as ‘antichlor’ in bleaching
4. Used as fixer in photographic work as ‘Hypo’

Sodium nitie

$NaNO_2$

It is a white to slightly yellowish crystalline powder that is very soluble in water and is hygroscopic.

Preparation

1. It can be prepared by strongly heating sodium nitrate

$$2NaNO_3 \rightarrow 2NaNO_2 + O_2$$

2. It is more conveniently made by heating the nitrate with lead

$$2NaNO_3 + Pb \rightarrow 2NaNO_2 + PbO$$

Chemical Properties

1. Above 330 °C sodium nitrite decomposes (in air) to sodium oxide, nitric oxide and nitrogen dioxide.

$$2\ NaNO_2 \rightarrow Na_2O + NO + NO_2$$

2. Sodium nitrite can also be used in the production of nitrous acid

Uses

1.Sodium nitrite is an efficient drug in case of cyanide poisoning. It is used together with sodium thiosulfate. It is on the World Health Organization's List of Essential Medicines.

2.From an industrial perspective, it is the most important nitrite salt. It is a precursor to a variety of organic compounds, such as pharmaceuticals, dyes, and pesticides.

3.It is probably best known as a food additive used in processed meats and (in some countries) in fish products.

ASTRINGENTS

❖An astringent is a drug which makes the cells shrink by precipitating **proteins from their surfaces.**

❖They are used in **lotions to harden and protect** the skin and to reduce bleeding from minor abrasions. Other preparations in which they are used are antiperspirant preparations,

❖ **mouth washes, eye drops, throat lozenges** etc.

POTASH ALUM (ALUMINIUM POTASSIUM SULPHATE)

$KAl(SO_4)_2.12H_2O$

Alum of the Pharmacopeia **(official in I.P. 1 966 and B.P. 1988)** is potash alum, i.e., double aluminium sulphate and potassium sulphate with 12 molecules of water of hydration.

Preparation: Potash alum is prepared by adding a hot; concentrated solution of potassium sulphate to a hot solution of an equivalent quantity of aluminium sulphate.

The solution is cooled and the alum crystallizes out. By crystallizing slowly it is possible to get large regular, octahedral crystals.

$$Al_2(SO_4)_3.18\,H_2O + K_2SO_4 \longrightarrow \underset{\text{Potash alum}}{2KAl(SO_4)_2.12H_2O} + 6H_2O$$

Physical and Chemical Properties

❖Alum occurs as large, octahedral**, colourless crystals** or in small crystals or as a white powder.

❖It is **without odour** and has a sweetish, strongly astringent taste. Alum is soluble in cold water but more soluble in hot water.

❖ Alum is transparent but it is sometimes opaque on the surface due to traces of basic salt being formed. When basic salt is present, alum will not give a clear solution.

❖When alum is heated it melts at **92^0 C** and loses all the water of hydration at **200^0C** leaving a white residue known as burnt alum containing anhydrous aluminium and potassium sulphates.

Medicinal and Pharmaceutical Uses

1.Alum precipitates proteins and protects and hardens the skin. It is used to prepare styptic pencil used for stopping the bleeding in small cuts.

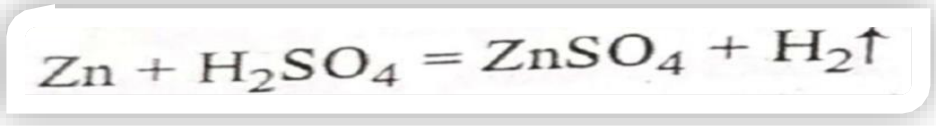
2.Since alum precipitates proteins, this property is made use of in preparing certain biological preparations such as alum precipitated tetanus toxoid and alum precipitated diphtheria toxoid.

3.Used in mouthwashes, gargles and antiperspirants deodorants.

ZINC SULPHATE

$ZnSO_4.7H_2O$

Preparation: It is prepared by boiling a slight excess of metallic zinc with dilute sulphuric acid.



Properties:

- Zinc sulphate occurs as colourless, transparent crystals or as a crystalline powder.
- It is odourless and has an astringent, metallic taste.
- It is efflorescent in dry air. It is easily soluble in water, insoluble in alcohol and soluble in glycerin. Aqueous solution of zinc sulphate is slightly acidic.

Uses:

1. Emetic **(induces vomiting)**: zinc sulphate is used as reflex emetics especially in narcotic poisoning (opium poisoning), for this 1% solution **contains 0.6 to 2 g given orally**.
2. Astringent: it is used externally for its antiseptic and astringent properties in powder and in lotions
3. It also serve as aid in **healing of wounds**

4. A 0.25 % zinc sulphate aqueous solution is used as an ophthalmic astringent.

References

- A.H. Beckett & J.B. Stenlake's, Practical Pharmaceutical Chemistry Vol I & II, Stahlone Press of University of London, 4th edition.

- Anand & Chatwal, Inorganic Pharmaceutical Chemistry

- P. Gundu Rao, Inorganic Pharmaceutical Chemistry, 3rd Edition
- Indian Pharmacopia 2018, volume I,II,III .
- https://www.sciencedirect.com/topics/medicine-and-dentistry/expectorant-agent
- http://rc.rcjournal.com/content/52/7/859
- https://link.springer.com/article/10.1007/s00520-004-0700-8
- https://link.springer.com/article/10.1007/s13181-018-0688-y
- https://www.tandfonline.com/doi/abs/10.3109/15563650.2012.742197
- https://www.ncbi.nlm.nih.gov/books/NBK507796/
- https://www.sciencedirect.com/topics/medicine-and-dentistry/astringent