PHARMACY INDIA

1st YEAR STUDENTS

MASTER NOTES FOR D.PHARMA

PHARMACEUTICAL CHEMISTRY

- Subject Wise Notes
- According To PCI Syllabus
- Easy To Understand
- Prepared By Experts
- Learn With Flow Charts

Chapter 1

Introduction to Pharmaceutical Chemistry

1. Introduction to pharmaceutical chemistry

- Scope
- Objectives

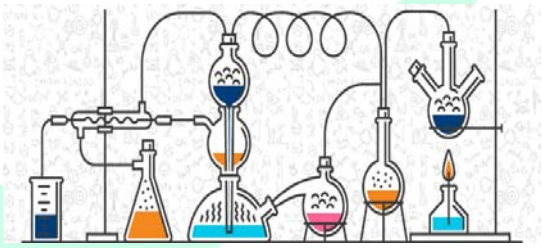
2. Sources and types of errors: Accuracy, Precision, Significant figures

3. Impurities in pharmaceuticals

- Sources and effect of impurities in Pharmaceutical substances
- Importance of Limit Test
- Principle and procedures of Limit tests for chloride
- Principle and procedures of Limit tests for sulphates
- Principle and procedures of Limit tests for iron
- Principle and procedures of Limit tests for heavy metals
- Principle and procedures of Limit tests for arsenic

INTRODUCTION TO PHARMACEUTICAL CHEMISTRY

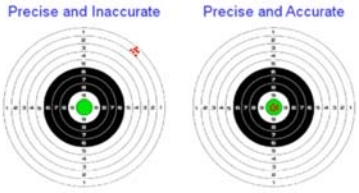
- Chemistry is the branch of science that deals with the properties, composition, and structure of elements and compounds, how they can change, and the energy that is released or absorbed when they change.
- The subject is further subdivided into various branches
  - Inorganic chemistry
  - Organic chemistry
  - Analytical chemistry
  - Physical chemistry
  - Phytochemistry
  - Medicinal chemistry
  - Biochemistry



- **Pharmaceutical chemistry:** Pharmaceutical (Medicinal) chemistry is a discipline at the intersection of chemistry and pharmacology that involves the identification, synthesis, and development of new chemical entities that are suitable for medical or pharmaceutical use.

Organic chemistry + Pharmacology = MEDICINAL CHEMISTRY

- **Inorganic Chemistry:** It is the branch of chemistry in which we study all the elements and their compounds except carbon and its compounds.



- Precision is the degree of closeness of the measurements with each other.
- Precision - often referred as Repeatability and Reproducibility error.
- Precision is getting consistent results of repeated measurements.

Significant Figures

- The significant figures of a number are digits that carry meaning contributing to its measurement resolution. This includes all digits.
- **Significant figures rules**

- All non-zero digits are significant.
- Captive zeros are significant.
- Trailing Zeros are only significant if there is a decimal point or a bar above a zero.
- Leading zeros are never significant.
- Exact numbers have an infinite amount of sig digs.

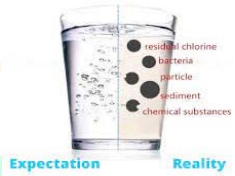
- Trailing zeros in a number containing a decimal point are significant. For example, 12.2300 has six significant figures: 1, 2, 2, 3, 0 and 0.
- The number 0.000122300 still has only six significant figures (the zeros before the 1 are not significant).

IMPURITIES IN PHARMACEUTICALS

- Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APL), or develop during formulation.
- The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products.

Sources of impurities

✓ Materials employed in manufacture.
✓ Method or the process used in manufacture.
✓ Chemical processes and the plant materials employed in the processes.
✓ Storage conditions.
✓ Decomposition.



Effect of impurities

➢ Almost pure substances are difficult to get and some amount impurity is always present in the material.
➢ So, the impurities which are present in the substances may have the following effects:
- Impurities may bring about incompatibility with other substances.
- Impurities may lower the shelf life of the substances.
- Impurities may cause difficulties during formulations and use of the substances.

➢ Sometimes Impurities changes the physical and chemical properties of the substances.

Procedure

Test Sample	Standard Sample
As per the monograph 25ml solution.	Take 2ml of lead solution and dilute it up to 25 ml with distilled water.
Add dilute acetic acid/ammonia to adjust the pH between 3 and 4.	Add dilute acetic acid/ammonia to adjust the pH between 3 and 4.
Add water up to 35ml.	Add water up to 35ml.
Add 10ml of H_2S solution.	Add 10ml of H_2S solution.
Dilute it up to 50ml with distilled water.	Dilute it up to 50ml with distilled water.
Stir immediately and compare the solution.	Stir immediately and compare the solution.

Observation

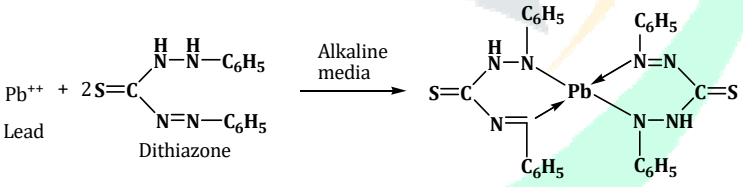
- The color produce in the sample solution should not be greater than standard solution.
- If color produces in sample solution is less than the standard solution, the sample will pass the limit test of heavy metals and vice versa.

Limit Test of Lead

Principle

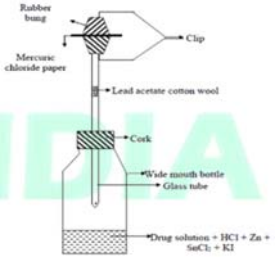
- Limit Test for Lead is based upon the chemical reaction between lead and diphenyl thiocarbazone (dithizone) in an alkaline solution to form lead dithizone, which is red.
- Dithizone itself is green in colour and the lead dithizone formed is violet in colour. Thus, the net resultant colour of the solution becomes red.
- To avoid interference by other metals and make the pH optimum, reagents like ammonium citrate, KCN, and $NH_2OH.HCI$ is employed.

Chemical Reaction



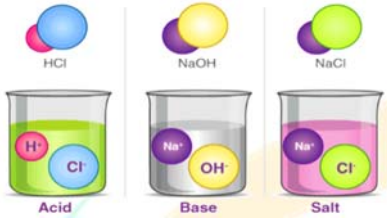
Procedure

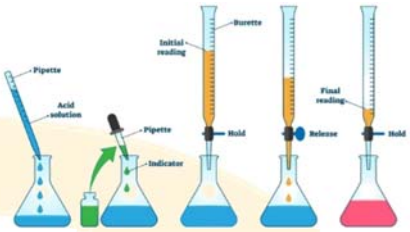
- Sample solution is transferred to a separating funnel.
- To it 6 ml of ammonium citrate, 2 ml potassium cyanide and 2 ml of hydroxalamine HCl are added.
- 2 drops of phenol red.
- Solution is made alkaline by adding ammonia solution.
- This is then extracted with 5 ml portions of dithizone solution until it becomes green.
- The combined dithizone extracts are shaken for 30 seconds with 30 ml of nitric acid and chloroform layer is discarded.
- To the acid solution 5 ml of standard dithizone solution is added and 4 ml ammonium cyanide and solution is shaken for 30 sec.
- Similarly prepare standard.



Observation

- In acid-base titrations, when solutions of alkali are titrated against standard acid solutions and the estimation of concentration an alkali solution using a standard acid solution is called Alkalimetry.





- Similarly, the estimation of concentration an acid solution using a standard alkali solution is called Acidimetry.

Acid base theory

- Theories of acid and base There are three theories which explain the concept of acid and base
  1. Arrhenius theory
  2. Bronsted-Lowry theory
  3. Lewis theory
- The **Arrhenius theory** of acids and bases states that "an acid generates H^+ ions in a solution whereas a base produces an OH^- ion in its solution".
- The **Bronsted-Lowry theory** defines "an acid as a proton donor and a base as a proton acceptor".
- Finally, the **Lewis definition** of acids and bases describes "acids as electron-pair acceptors and bases as electron-pair donors".

Types of Acid-Base Titrations

S.NO.	TYPES	EXAMPLES
1.	Strong acid-strong base	Hydrochloric acid and sodium hydroxide
2.	Weak acid-strong base	Ethanoic acid and sodium hydroxide
3.	Strong acid-weak base	Hydrochloric acid and ammonia
4.	Weak acid-weak base	Ethanoic and ammonia

Acid-Base Indicators

- Acid-base indicators can be broadly classified into three groups.
  1. The phthalein and sulfo phthalein (e.g., Phenolphthalein).
  2. Azo indicators (e.g., Methyl orange).
  3. Triphenylmethane indicators (e.g., Malachite green)

The Choice of Indicators based on the type of Titration is tabulated below

S.NO.	TYPES OF TITRATIONS	INDICATORS
1.	Strong acid-strong base	Phenolphthalein is usually preferred because of its more easily seen colour change.
2.	Weak acid-strong base	Phenolphthalein is used and changes sharply at the equivalence point and would be a good choice.
3.	Strong acid-weak base	Methyl orange will change sharply at the equivalence point.
4.	Weak acid-weak base	Neither phenolphthalein, nor methyl orange is suitable. No indicator is suitable because it requires a vertical portion of the curve over two pH units.

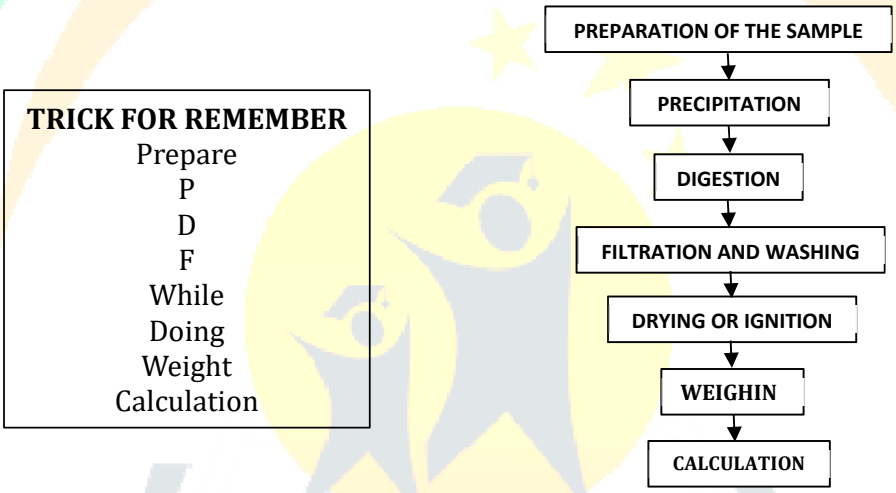
Principle

- A general principle of gravimetric method of analysis is based on a chemical reaction between analyte and reagent.

$$aA + rR \longrightarrow Aa\,Rr$$

- The analyte (A) of molecules 'a' react with the reagent (R) of molecule 'r'. After drying, the product formed by igniting AaRr can either be weighed or ignited to create another compound of known chemical components.

Steps involved in Gravimetric Analysis



Preparation of the sample

- Sample solution is prepared for the analysis, precipitation should be carried out in dilute solution.
- Adjustment of the volume, appropriate pH and getting the desired properties of the solution for the precipitate is taken care in this step.

Precipitation

- This step requires addition of the precipitating agent in the form of solution to the sample solution.
- After addition of the first drop of the precipitating agent , supersaturation occurs and nucleation starts to occur , where molecules of precipitate aggregate together and forms a nucleus.

Digestion

- Let precipitate stand in contact with the solution from a which it was precipitated usually at high temperature.
- The small particles tend to dissolve and precipitate on the surfaces of the larger crystals.
- This process is called as digestion.

Filtration and washing

- It is crucial to wash the precipitate very well in order to remove all adsorbed species which will increase the weight of the precipitate.
- Dilute nitric acid, ammonium nitrate, or dilute acetic acid may be used for washing.

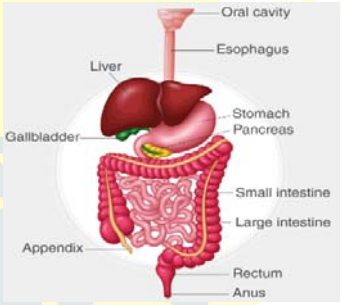
- It should be stored in air tight container at room temperature.

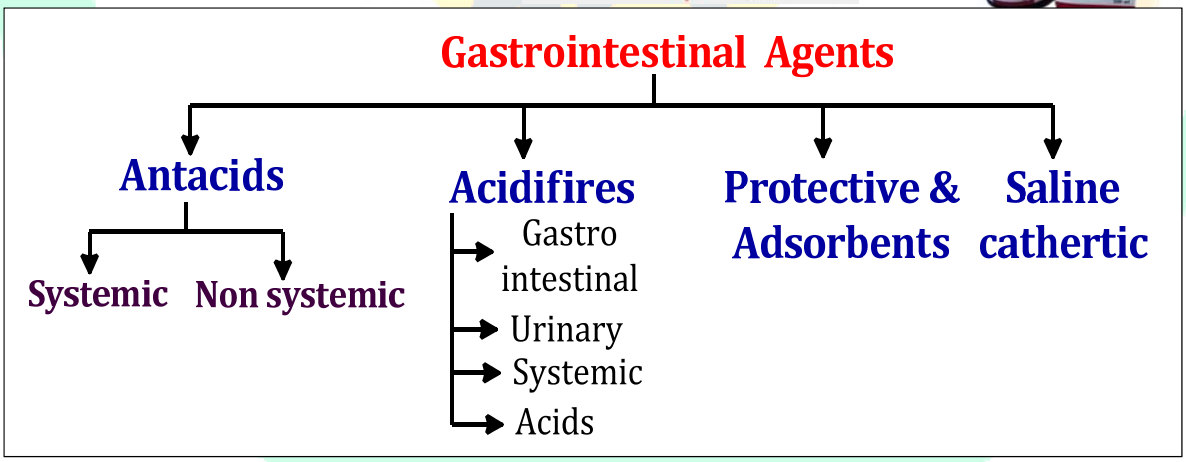
Uses

- As a dietary iron supplement
- To treat iron deficiency anaemia

GASTRO-INTESTINAL AGENT

- The Gastrointestinal tract includes the mouth, stomach, small intestine, large intestine, rectum & anus.
- Gastrointestinal agents include many different classes of drugs that are used to treat gastrointestinal disorders
- Gastrointestinal agents are used in the treatment of Gastric Acidity, Peptic Ulcers, and Gastro Esophageal Reflux Disease (GERD), Bowel Motility Disorders, Constipation, and Diarrhea, and for the treatment of Nausea and Vomiting.





Antacids

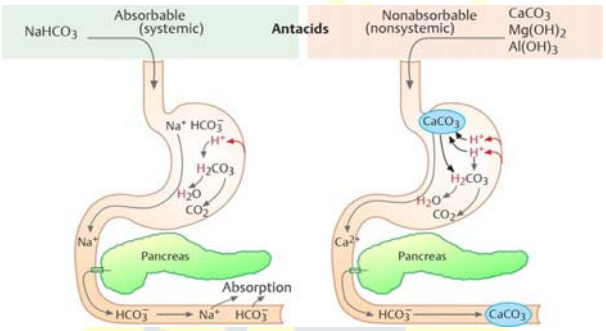
- Antacids (anti - against; acidus - acid) are weak alkaline compounds used to neutralize hydrochloric acid in the stomach.
- Antacids are the substances which reduce gastric acidity resulting in an increase in the pH of stomach and duodenum.

Classification of Antacids

Non-systemic antacids	Systemic antacids

• Non-systemic antacids are compounds that are not absorbed into the systemic circulation • Their anionic group neutralizes the H+ ions in gastric acid. • This releases their cationic group which combines with HCO3– from the pancreas to form an insoluble basic compound that is excreted in feces.	• Systemic antacids are absorbed into the systemic circulation • They have a cationic group that does not form insoluble basic compounds with HCO3–.
➢ Aluminum Hydroxide ➢ Magnesium Hydroxide	➢ Sodium bicarbonate

Mechanism of Antacid



ALUMINUM HYDROXIDE GEL

❖ **Chemical formula:** $Al(OH)_3$
❖ **Molar mass:** 78.00 g/mol.
❖ **IUPAC name:** Aluminium hydroxide
❖ **Synonyms**: Hydrargillite

Physical properties

➢ **Appearance:** White amorphous powder
➢ **Odor:** Odourless
➢ **Taste:** Tasteless

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

$$3Na_2CO_3 + 2KAI(SO_4)_2 + H_2O \longrightarrow 3Na_2SO_4 + K_2SO_4 + 2Al(OH)_3$$

Uses

- Aluminium hydroxide used as gastric antacid.
- Aluminium hydroxide used in treatment of Gastro esophageal reflux disorder.

- It is defined as gases which are manufactured packed and intended for giving to a patient for diagnosis , therapy and to produce anaesthesia.
- It is considered as drugs and their use without medical practitioner is unsafe.

- Inhalants are the gaseous substances which are , taken into the body by way of the nose and trachea
- Oxygen , carbon dioxide and nitrous oxide are the gases used as inhalants.

OXYGEN

- Chemical formula – O_2
- Molecular wight - 32

❖ PREPARATION

- The main laboratory method of producing oxygen is the electrolysis of aqueous solutions of alkalies or acids.
- Here the hydrogen ions migrate toward the cathode , where they gain an electron and transform into neutral atoms forming hydrogen molecules.
- The hydroxide ions become discharged at the anode with the formation of water and oxygen.

$$2H_2O \leftrightarrow 2H^+ + 2OH^-$$

$$\text{At cathode } 2H^+ + 2e^- \rightarrow 2H$$

$$2H \rightarrow H_2\uparrow$$

$$\text{At anode } 2OH^- - 2e^- \rightarrow H_2O + O$$

$$O \rightarrow \tfrac{1}{2} O_2 \uparrow$$

❖ PROPERTIES

- It is an odourless , tasteless gas.
- It is soluble in water and in alcohol at normal temperature and pressure.
- Oxygen gas can be liquified at low temperatures and under high pressures.

❖ STORAGE

- Store under compression in metal cylinders.
- The cylinder of oxygen are painted black with a white shoulder .

❖ USES

- Oxygen is required for respiration of human beings.
- Oxygen is given by inhalation to correct hypoxaemic conditions in chronic bronchitis , pneumonia or pulmonary edema, etc.
- It is valuable in the treatment of carbon monoxide poisoning.
- It is used as a diluent of volatile and gaseous anesthetics.

CARBON DIOXIDE

- Chemical formula - CO_2
- Molecular weight – 44.01

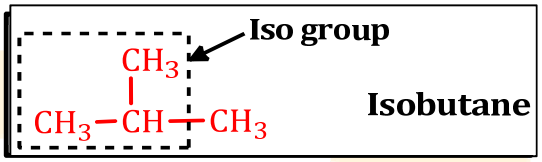
❖ PREPARATION

- Carbon dioxide is made during the heating of lime – stone to produce quicklime for the building grade.

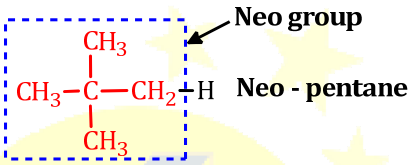
CH_3-CH_2-CH_2-CH_3 - ***n-butane***

CH_3-CH_2-CH_3 Propane [n is not used because it has only one structure]

(b) Prefix iso: It is used when one methyl group is attached to the second C-atom of the continuous chain.



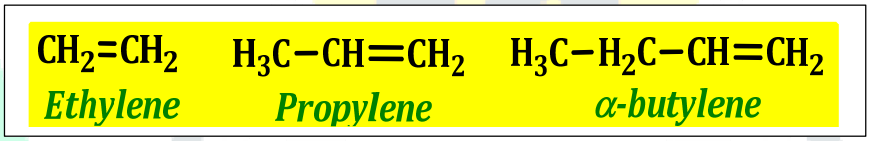
(c) Prefix neo: When two methyl groups are attached to the second C-atom of the continuous chain.



Neo' is used when minimum 5 carbon atoms are present.

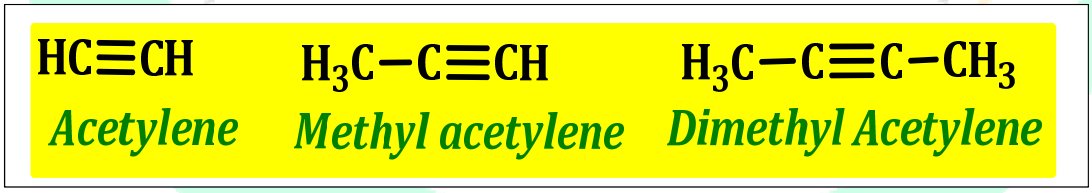
2. Common names of Unsaturated Hydrocarbons:

(a) **Compounds Containing Carbon - Carbon double bond:** These are called alkylene or olefins (General formula CH_2).



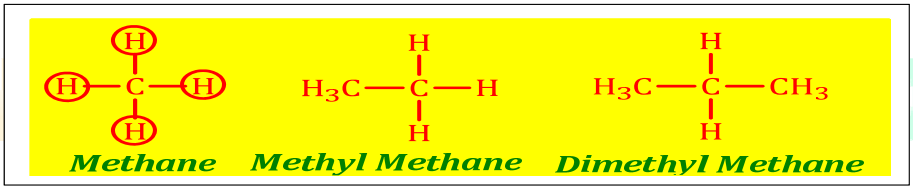
(b) Compounds Containing Carbon - Carbon triple bond: (General Formula is C_nH_{2n-2})

- There names are derived by replacing H-atoms of acetylene by alkyl group.



Derived Name System

- In a homologous series the homologues are considered to be the derivative of the famous homologue.

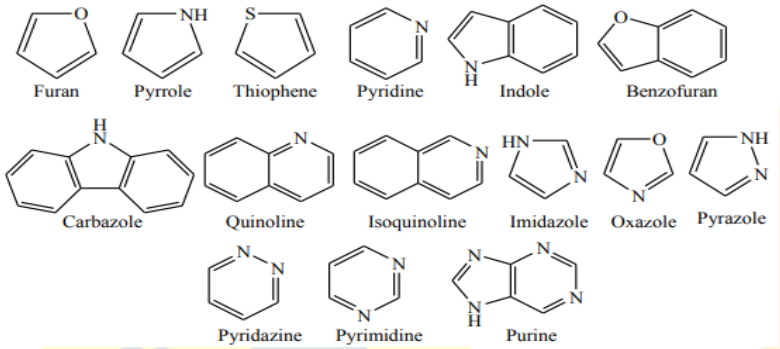


- First homologue of alkane series encircled H atom will be replaced by any substituents/functional group.
- Similarly: CH_2=CH_2→ Ethylene is the first homologue of the alkylene series.

- It should be cyclic.
- It should be planar.
- It should not contain any sp3 hybridised atoms.
- It must have (4n+2) **π** electrons.
- Aromatic Heterocyclic compounds are analogous to Benzene.
- Examples: Furan, Pyrrole, Thiophene, Indole, Benzofuran, Carbazole, Quinoline, Isoquinoline, Imidazole, Oxazole, Pyrazole, Pyridazine, Pyrimidine, Purine, etc.

☐ AROMATIC HETEROCYCLIC COMPOUNDS

Example



HANTZCH-WIDMANN SYSTEM OF NOMENCLATURE

- This nomenclature system specifies the nature, position, ring size, number, and types of heteroatoms present in any heterocyclic compounds.
- This system of nomenclature applies to monocyclic three-to-ten-membered ring heterocycles
- The nomenclature of heterocyclic compounds are assigned by combining 'prefix' (that indicate the heteroatom present) with 'stem' (that indicate the ring size as well as the saturation and unsaturation in the ring) and 'suffixes'.

Prefix + Stem + Suffix

❖ Common Prefix for Heteroatoms (arranged in the preferential order)

HETEROATOM	SYMBOL	PREFIX
Oxygen	O	Oxa
Sulphur	S	Thia
Selenium	Se	Selena
Nitrogen	N	Aza
Phosphorous	P	Phospha
Arsenic	As	Arsa
Antimony	Sb	Stiba
Bismuth	Bi	Bisma
Silicon	Si	Silia
Tin	Sn	Stanna
Lead	Pb	Plumba

Introduction

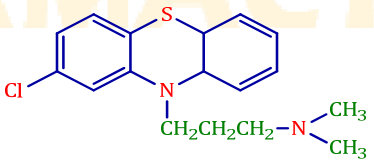
- The psychopharmacological agents or psychotropic drugs are those having primary effects on *psyche* and used for treatment of psychiatric disorders.
- Antipsychotics also called as ataractics, neuroleptics are the drugs which calm psychotic patients, reduce psychotic manifestations or illness by acting on the central nervous system by a depressant action.

Classification of Antipsychotics

Class	Sub-class	Drugs	Mechanism of action
Phenothiazines	Aliphatic side chain	Chlorpromazine, Triflupromazine	Mainly block the D2 receptor (phenothiazine and thioxanthene also block D1, D3 and D4)
	Piperidine side chain	Thioridazine	
	Piperazine side chain	Trifluoperazine, Fluphenazine	
Butyrophenones	Haloperidol Trifluperidol Penfluridol		
Thioxanthenes	Flupenthixol		
Other heterocyclics	Pimozide, Loxapine		
Atypical antipsychotics	Amisulpiride, Zotepine		
	Clozapine		It blocks the 5HT 2A, and α adrenergic receptor.
	Olanzapine		It blocks the 5HT 2A, D2 and α adrenergic receptor.
	Risperidone		It blocks the H1, 5HT-2A D2 and α adrenergic receptor.
	Quetiapine		It blocks the H1 5HT2, 5HT1, D2 and α adrenergic receptor.
	Aripiprazole		It blocks partially $5HT_{1A}$, D2 but antagonist 5HT2
	Ziprasidone		Atypical antipsychotic with combined D2 + 5HT 2A/2C +H1+α1 Blockage activity and antagonist action at $5HT_{1D}$ + agonistic activity at $5HT_{1A}$

CHLORPROMAZINE HYDROCHLORIDE

- Chlorpromazine is used in the treatment of both acute and chronic psychoses, including schizophrenia and the manic phase of bipolar disorder.



➢ **Brand names**: Largactil, Megatil, Emetil, Thorazine

Uses

1. Parenterally it is used as a vasopressor for treating and preventing acute hypotensive state arising due to spinal anaesthesia.
2. It is also used in severe hypotension occurring from traumas which induce shock.

Stability and Storage:

- Not stored above 25°C.
- Stable between 2°C-8°C.

Brand name: Aramine.

Formulation: Metaraminol tablets.

ADRENERGIC ANTAGONIST

Introduction

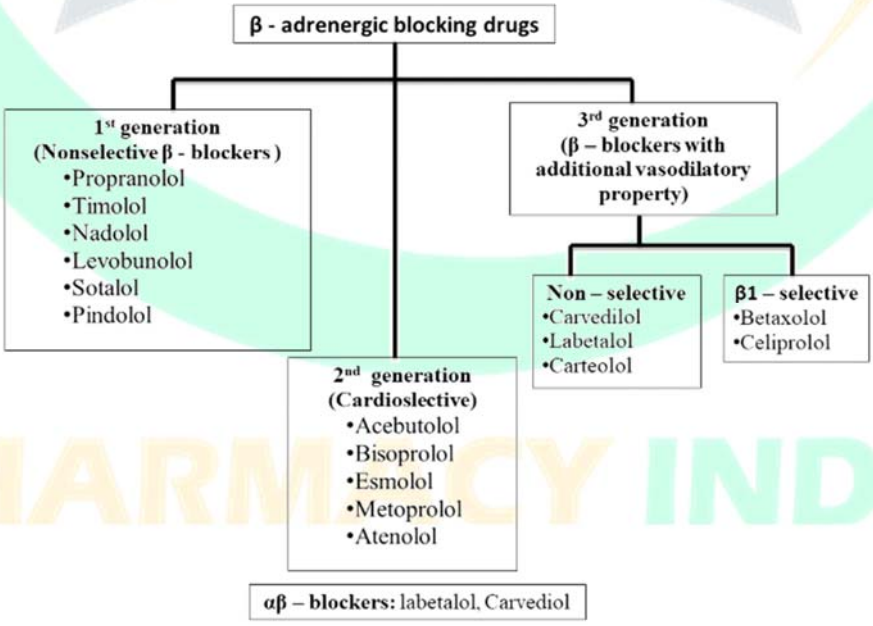
Drugs which antagonize the actions of sympathomimetic or adrenergic neurotransmitters are called sympatholytic or anti-adrenergic drugs. They are also known as sympathetic blocking agents.

Classification

α - Adrenergic blocking drugs

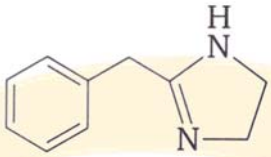
Class	Drugs
Nonequilibrium type	
β-Haloalkylamines	Phenoxybenzamine (**irreversible α1 and α2 blocker**)
Equilibrium type (competitive)	
Nonselective	**Ergot alkaloids** — Ergotamine, Ergotoxine
	Hydrogenated ergot alkaloids — Dihydroergotamine (DHE), Dihydroergotoxine
	Imidazoline — Phentolamine
	Miscellaneous – Chlorpromazine
α1 selective	Prazosin, Terazosin, Doxazosin, Alfuzosin, Tamsulosin
α2 selective	Yohimbine

β - Adrenergic blocking drugs



TOLAZOLINE

Synonym: Priscoline
Chemical name: 2-Benzyl-2-imidazoline.

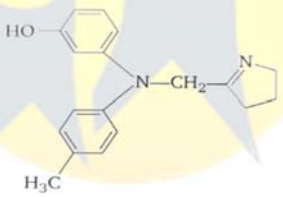


Properties
- White, bitter powder with characteristic odour.
- Soluble in water.

Uses
- To treat Raynaud's syndrome.
- Peripheral vasospasm.

Formulation: Tolazoline Injection.
Brand name: Priscohine hydrochloride

PHENTOLAMINE (REGITINE)
- Phentolamine is a competitive a-adrenergic antagonist.
- It is a synthetic imidazoline.
- It binds to a-1 and a-2 receptors resulting in a decrease in peripheral vascular resistance and vasodilation.



Chemical name: 3-[(4, 5-Dihydro-1H-imidazol-2-ylmethyl) (4-methyl phenyl)amino] Phenol.

Uses
- Phentolamine is used for diagnosing Pheochromo cytoma (Tumours of adrenal medulla)
- It is also used to prevent dermal necrosis.
- It is used for conditions like decrease in impedance of left ventricular ejection.

Stability and storage:
- Phenotlamine mesylate.
- Injection is stable for 2 days at room temperature.

Brand name: Oraverse, Regitine, Fentanor.
Formulation: Phentolamine injection.

PHENOXYBENZAMINE
- Phenoxybenzamine is a nonselective a-blocked.
- Phenoxybenzamine is a-adrenergic antagonist with long duration of action.
- It is used as an anti-hypertensive and as a peripheral vasodilator.