Natubhai V. Patel College of Pure & Applied Sciences

T. Y. B.Sc. (Industrial chemistry)

IC – 302: Unit Process, Synthetic dyes and Pharmaceuticals

UNIT – 5

Syllabus

Drugs introduction: Drugs, pro-drugs, biotransformation of drugs, routes of drugs administration and dosage forms, drug binding, drug toxicity, drug addiction, some important terms used in chemistry of drugs, biological and medical terms used in the study of drugs, distinctive definition. Classification of drugs, relation of chemical structure and chemical activity, Account of Sulfa drugs, Antipyretics and analgesics

5.0 INTRODUCTION

5.1.1 DRUGS

The word '**drug**' is derived from the French word "**drogue**" which means a **dry herb**. In a general way, a drug may be **defined as substance used** in the **prevention, diagnosis, treatment** or **cure of disease** in man or other animals. According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the recipient.

An ideal drug should satisfy the following requirements

- When administrated to the ailing individual or host, its action should be localized at the site where it is desired to act. In actual practice, there is no drug which behaves in this way. It generally tends to distribute itself anywhere in the tissues of the host.
- It should act on a system with efficiency and safety.
- It should not have any toxicity.
- It should have minimum side effects.
- It should not injure host tissues or physiological processes.
- The cells should not acquire tolerance or resistance to the drug after some time. In actual practice, the cells which were originally susceptible to the action of a particular drug may after sometime acquire a tolerance or resistance to that drug.

Very few drugs satisfy all the above conditions. However, the search for ideal drug continues.

5.1.2 PRODRUG

A **biologically active drug** which by **latentiation** is converted into an **inactive carrier** form is called a pro-drug.

Prodrug on reacting with enzyme or non-enzyme compound, releases the active compound (drug). Latentiation of drug produces;

- Prolongation of action
- Shortening of action
- Drug localization
- Transport regulation
- Adjuncts to pharmaceutical formulation.
- Lessening of toxicity and side effects.

5.1.3 BIOTRANSFORMATION OF DRUGS

The drugs are **converted into pharmacologically active metabolite** by biotransformation. These metabolites are highly active. This activity contributes to pharmacological effect ascribed to the parent drug. In some cases inactive parent drug gets converted to biologically active metabolite. Since all the metabolites are not non-toxic, many toxic side effects like tissue mercrosis, carcinogenicity are observed. The formation of water soluble metabolite enhances drug elimination and pharmacologically inactive, non-

toxic and polar compound formation. Most of the drugs undergo metabolic transformation in the body. The **main site** of **metabolism** is **liver**.

Genetic differences, species differences, age, sex, nutritional and hormonal factors, pathological states and stress influence the rate and extent of drug biotransformation and thus, influence the duration and extent of pharmacological activity.

5.1.4 ROUTES OF DRUG ADMINISTRATION AND DOSAGE FORMS

The rate of drug absorption in the body is decided by the route of administration. The common routes in the increasing order of rapidity of absorption in man are **oral, subcutaneous, intramuscular, inhalation** and **intravenous**. The speed of absorption of drug can be altered by a number of pharmacological and chemical manipulations. The injected drug is carried, away from injection site by circulation. During circulation drug passes through many barriers and survives and reaches the site of action (cell receptors) where the required biological response is developed. Drug administration by the intravenous the intra arterial, the intra spinal or intra cerebral routes introduces the drug directly to the body fluids and thus avoids complication in drug absorption.

Drugs are prepared and used in chemically pure form. Dosage of drugs are calculated in appropriate weight units.

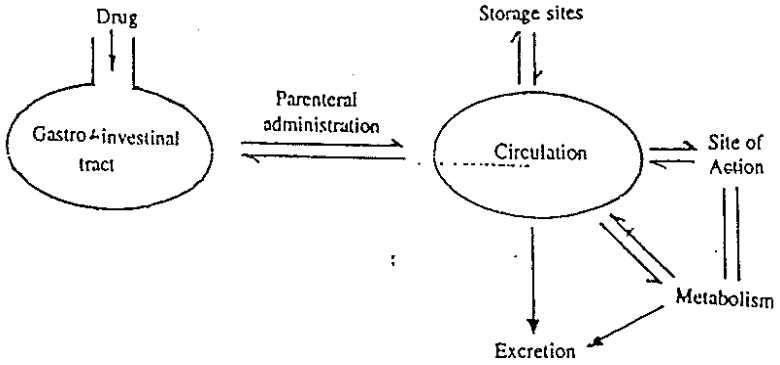


Figure: Schematic representation of drug administration followed by the transfer of drugs from various compartments.

Drug is **modified** according to the requirement for the effective drug accessibility to the active site as follows:

- **Change in the dosage form** in which the drug is formulated. Dosage form modification influences the therapeutic response. It is a physical change.
- **Alteration of chemical structure** of the drug molecule to hinder or enhance the biological effect. It is a chemical modification.
- **Modes of administration**: The routes of administration (for example oral, intravenous or intra muscular) as well as the time of administration and interval between the dosages can affect the therapeutic response to a drug.

Drug enters into the body at the point of administration of the body. Which depends on the dosage form to the receptor site or biophase,(the phase at the site of action of the drug in the organism).

5.1.5 DRUG BINDING

Extensive **drug binding** in the body **occurs in the blood**. Blood contains **6.5%** of **protein** of which **50%** is **albumin**. It is mainly involved in drug binding. Its molecular weight is 69000 and it has net negative charge at **blood pH 7.4**. It can interact with anions and cations also. The drug-protein binding may be due to ion-ion interactions, hydrogen bonding and hydrophobic and vander Waal's-forces. This protein drug binding is usually reversible reaction.

$(P) + (D) \rightleftharpoons (PD)$ where (P) = free protein concentration.
(D)= free drug concentration
(PD)= drug-protein complex.

The drug binding resembles salt formation. This protein binding acts as a transport system for the drug, which while bound is hindered in its access to the site of metabolic action and excretion.

5.1.6 DRUG TOXICITY

Drug administration is always followed by the expected reaction. It is many a time associated with **other side reactions**; considered **to be toxic reactions**. This may range from a **mild skin rash** though more serious complications like **blood dyscrasias** (abnormality in the blood picture) and **liver damage** may occur. Drugs show **short term (acute)** and **long term (chronic)** toxicity.

5.1.7 DRUG ADDICTION

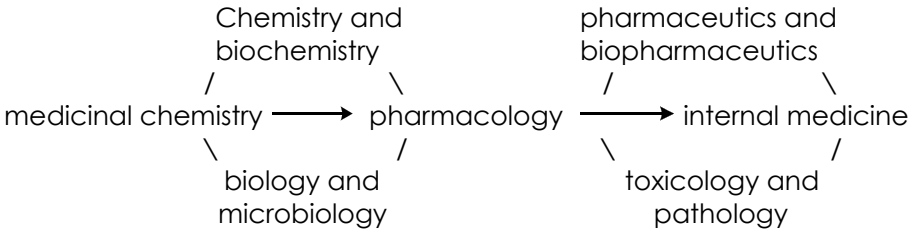
After **discontinuation of drug** administration, the tolerance acquired by the individual disappears at a rate varying for each-individual and each drug. The body cells readjust to the absence of drug unnoticeably. In some cases after the drugs withdrawal, a psychic craving for the drugs is observed, which leads to physical disturbances. This syndrome is called "addiction." Certain drugs, for example morphine related compounds, cocaine, and under certain conditions barbiturates have a notable potentiality for causing addiction.

5.2 SOME IMPORTANT TERMS USED IN CHEMISTRY OF DRUGS

5.2.1 Medicinal Chemistry

Medicinal chemistry has been aptly defined by Dr. Glenn Ullyot as a field which applies the principles of chemistry and biology to the creation of knowledge leading to the introduction of new therapeutic agent. Hence the medicinal chemist must not only be a competent **organic chemist** but he must have a **basic background** in the **biological sciences**, especially biochemistry and pharmacology.

The relationship of medicinal chemistry to other disciplines has been indicated by the following diagram:



The basis of understanding in the medicinal chemistry lies in an awareness of the relationships between the chemistry of a particular compound or group of compounds and their interactions with the body which are known as structure-activity relationships, and the mechanism by which the compound influences the biological system, which is known as its mode of action. The objective of these studies is to improve the beneficial or therapeutic effects of a drug, whilst at the same time minimizing undesirable side-effects.

5.2.2 Pharmacy

The clinician does not administer a pure compound, but a complex formulation, of which the active constituent agent forms only a small part. **Pharmacy** is the **study of** the **formulation** of an **active chemical entity**; which is also known as the active principle The drug so formed is the vehicle which is then considered most appropriate for the administration of a particular therapy; such '**vehicles**' are in the forms of tablets, capsules, powders, suppositories and aerosols.

In general, the tablet form is preferred because this '**package**' is usually the **simplest to** manufacture, transport, handle and imbibe, and is frequently the most suitable form for long-term storage. The active principle is only a small proportion of the whole tablet, whose bulk is composed of fillers and binders designed to hold the tablet together, and agents which are added to break up the tablet efficiently in the patient's gastro-intestinal tract.

The pharmacist must produce a compressible mixture having high flow properties giving a hard tablet which can be able to withstand shock, shaking together etc., and which will nevertheless rapidly disintegrate after being swallowed.

5.2.3 Pharmacology

This science is the **study of the effects** of **pharmaca** or **biologically active substances on** the **animal system.** It is restricted to therapeutic agent or drugs, because it is also

applicable to all active agents; that is, fungicides, insecticides, toxins, etc. which affect the living body.

Essential requirements for the discovery of any new therapeutic agent for man are the **understanding of drug action** and the **design of testing procedures**. These two elements will allow experimental drugs to be applied and evaluated against a disease-simulated process in animal models or in isolated tissue fragments which in turn can be related to a human disease or disorder. There are inherent problems in the process, for, example the extrapolation of simulated conditions from animal experiments to man, and the inevitable imprecision of these experiments because of biological variation. The lack of accuracy arises because animals of any one species are non-identical, resulting in an individual and sometimes unpredictable variation in response to the pharmaca.

The word pharmacology is derived from the greek words "**pharmakon**" (drug) and "**logos**" (a discourse or treatise), and hence includes such allied fields, as pharmacy, pharmacognosy, toxicology, posology, chemotherapy, therapeutics and materia medica.

5.2.4 Molecular Pharmacology

Molecular pharmacology is the study of the **action of drugs** at the **molecular level**. The pharmacologist attempts to define the site of action of the drug; which is known as its receptor; then study the effect of the drug in the whole animal. He then makes an attempt to elucidate the precise sequence of the chemical and biological events concomitant with this drug receptor interaction. This approach has been found to be much less susceptible to the biological variations which occur in the animal system as a whole. It is therefore possible to get more consistent data on **drug-tissue interactions**, and as a result of this we can ascertain more precisely the **structure-activity relationship**. It is possible to prepare fragments of tissue from en animal to which a drug may bind. The degree of binding is then a measure of the ability of the drug to stimulate the tissue. The characteristic has been uncomplicated by other factors involved in the transport of the drug from its site of administration to the active site in the whole animal. It must of course be established that the tissue being examined has been fundamental to the action of the drug in the animal.

5.2.5 Pharmacodynamics

It is concerned with the **response of living organism** to **chemical stimuli** in the **absence of disease**. Knowledge of pharmacodynamics often is essential as a basis of pharmacotherapy. Because it is frequently **impossible** to produce in animals the **pathologic conditions identical** with **diseases** which occur in man, the pharmacologist may be called upon to study the pharmacodynamic activity of a chemical compound and, through his skill and experience, to prognosis as to its possible use as a therapeutic agent in the treatment of disease in man.

5.2.6 Pharmacophore

The physiological activity of drugs has been, found to depend upon the **presence** of particular **functional groups** or **structural units**. Such a part of the drug which causes the actual **physiological effect** is known as **pharmacophore**.

When a pharmacophore is introduced into biological inactive compound, this makes the compound biologically active many times. Thus, it is possible to make the compounds biologically active but less toxic by introducing various pharmacophores. **E.g.** alkyl, hydroxy, alkoxy, aldehyde or ketone, halogens and unsaturated lipids.

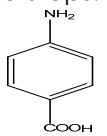
5.2.7 Pharmacodynamic agents

The drugs which **stimulate** or **depress** various **functions** of the **body** so as to provide relief from symptoms of discomfort are known as pharmacodynamic agents. Although these agents have a characteristic effect on the animal, they are not specific remedies for particular diseases. These agents are mainly used in the case of non-infectious diseases, to correct abnormal functions. However, they have no action on infective organism which causes the disease. Examples of pharmacodynamic agents are analgesics, sedatives, anesthetics, anti-histamines etc.

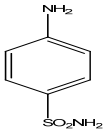
5.2.8 Antimetabolites

The substance which takes part in **cellular metabolic reactions** is known as metabolite. A chemical agent which **blocks the metabolism** due to its close structural similarity to the metabolite is known as **antimetabolite**.

An antimetabolite acts either by preventing the combination of the metabolite with its specific enzyme or combining itself with the enzyme to form a compound which is metabolically inactive or harmless to the cell. An interesting example of antimetabolites is sulphonamides. Its antibacterial activity is due to its structural analogy with p-amino benzoic acid (PABA) which is an essential metabolite. When the bacteria lake up sulphonamide, they cannot carry out the function of PABA and thus the metabolism is blocked and the growth of bacteria stops.



PABA



Sulfonamide

Some other examples of antimetabolites are methotrexate, a folic acid antagonist, and mercaptopurine, a purine antogonist. These are used in the treatment of leukaemia.

5.2.9 Bacteria

These are a group of micro-organisms which are **unicellular** and **surrounded** by rigid, complex, protein **cell wall**. These may be free living, saprophytic or parasitic; some are pathogenic to man, animals and plants.

Bacteria are **classified** into two types,

- Gram-positive
- Gram-negative

Method developed by **Christian Gram** which is as follows

In this method, the fixed bacterial, smear is first treated with a solution of crystal violet and then with iodine solution, which reacts with the dye and the cell constituents. The smear is then washed with alcohol (decolorizing agent) and safranin or some other counter stain is added.

The bacteria which retain the colour of crystal violet and appear deep violet (in colour) are called Gram-positive bacteria, whereas those which lose the violet colour and get counterstained by safranin and appear red in colour are called gram-negative bacteria. The following are some of the disease causing bacteria classified in this manner:

Gram +ve bacteria	**Gram —ve bacteria**
Diphtheria bacillus	Coli and typhoid bacillus
Leprocy bacillus	Gonococcus
Pneumococcus	Meningococcus
Staphylococcus	Plague bacillus
Streptococcus	Spirochaetes
Tubercle bacillus	Vibrios (V. Cholerae)

5.2.10 Virus

These are very small **micro-organisms** which are **parasitic within living cells**. These differ from bacteria in having only one kind of nucleic acid, either DNA or RNA, in lacking the apparatus necessary for energy production and protein synthesis and by not reproducing by binary fission but by independent synthesis of their component parts which are then assembled. These can multiply in a living tissue or tissue culture but not in artificial culture medium.

Virus may cause many kinds of acute and chronic diseases in man and can also cause tumours in animals.

5.2.11 Fungi (singular-fungus)

It is a **low form** of **vegetable life** including many microscopic organisms. It does not contain chlorophyll and generally grows on organic matter like leather, stale food, sugar, fruit, etc. Houses many superficial and systemic diseases in living beings.

5.2.12 Actinomycetes

Streptomycin was the **first antibiotic** of practical significance to be **isolated** from the class of organisms known as **actinomycetes**. This family of organisms differs from the moulds

that produce penicillin or the bacterium that yields tyrothricin. Actinomycetes grow as branching rods that many form filaments; they are smaller than the filaments of penicillium.

5.2.13 Mutation

The **sudden alteration** of a **gene** is known as **mutation**. This may be **spontaneous** or **induced** and is inherited by subsequent generations and remains until a further mutation occurs. Spontaneous mutation takes place without apparent influence from outside the cell while induced mutation is produced by a known agent outside the cell, e.g., ultraviolet radiation, X-ray etc.

5.2.14 Chemotherapy

The treatment of **infectious disease** by using a **chemical agent** is called chemotherapy. The substance so employed is referred to as chemotherapeutic agent. These agents are designed in such a way that they kill or destroy the disease producing organisms without any harmful effect on the cells in which organisms are present.

5.2.15 Peripheral Nervous System

The **nervous system** in the higher animals can be **divided into**

- Central nervous system (CNS)
- Peripheral nervous system consisting of somatic and autonomic nerve fibers.

The CNS **receives** various information, **decodes** them and then **sends instructions to** various peripheral tissues to produce appropriate reactions. The reaction pattern may be somatic as indicated by various types of body movements or may be autonomic (self-governed) which cannot be controlled at will, as indicated by changes in respiration, circulation visceral functions.

5.2.16 Neuron Transmitters

The **transmission** of the **instructions** (message) along a nerve is through **electric impulses**. Neurons are structural units of nervous system comprising of fibers which convey these electric impulses to the nerve cells. However, the end of the nerve fibers does not make a direct contact with the effector nerves (neurons), i.e., a nerve ending in a muscle, gland or organ. The point of communication between two adjacent neurons is called a synapse. As soon as electric impulse reaches a synapse, it causes a release (at the nerve ending) of a chemical substance which bridges the gap and forms a stimulus to conduct the impulse to next neuron. These **chemicals** which **help in the transmission** of **electric impulse** from one neuron to the next are called **neuron transmitters**.

5.3 BIOLOGICAL AND MEDICAL TERMS USED IN THE STUDY OF DRUGS

5.3.1 Pharmacon

This term has originated from the Greek word "**pharmacon**" meaning a **drug**.When a pharmacophore is **introduced** into a **biologically inactive substance**, then it is possible to make the compound **biologically active**. By introducing suitable pharmacophore it is even possible to make a drug less toxic than otherwise. **E.g.**; groups like alkyl, hydroxy, alkoxy, aldehyde, ketone, halogen etc

5.3.2 Receptor

It is the portion of the molecule or structure with which the **therapeutically active** compound **interacts**, producing series of events leading to an observable response. Some structurally specific drugs after interacting with specific cellular components (known as a receptor) form a complex with the receptor. Chemically receptor is a chemical structural component and biologically receptor is a micro- anatomical term.

5.3.3 Affinity

Drug-receptor interaction is due to complimentary structural characteristic that combines a drug with receptor, which initiates the response. The response is related to the number of **drug-receptor complexes**. Affinity is determined how much of the drug receptor complex is formed.

5.3.4 Intrinsic activity

Intrinsic activity or efficacy is a measure of the **ability** of the **drug-receptor complex** to **produce** the **biological effect**. Some drugs act as agonist and other drugs with similar structures act as antagonist. Only agonist has the ability of giving origin to stimulus that is intrinsic activity. While antagonists are the drugs that bind strongly to the receptor due to their great affinity for them but are devoid of activity.

5.3.5 Bio-isosters

Bio-isosters are the isosteric compounds which have the same type of biological activity.

Isosters are atoms, ions, or molecules in which peripheral layers of electrons are considered to be identical. These isosters which are iso-electric shows great similarity in properties. For example some isosters are CO and N_2, CO_2, and N_2O, N_3^- and $NCOO^{2-}$ and I^-, Ne and Na^+ Mg^{2+} and Al^{3+} and anions ClO_4^-, SO_4^{2-}, PO_4^{3-}

5.4 DISTINCTIVE DEFINITIONS

5.4.1 Antibiotics

Antibiotics are specific chemical substances derived from or produced by living organisms, which in small concentrations are capable of inhibiting the life processes of micro-organisms.

5.4.2 Antibacterial

Antibacterial agents are the drugs used in the treatment of infections ceased by bacteria. According to the effect produced, antibacterial agents can be **bacteriostatic** (inhibit growth of bacteria), or **bactericidal** (kill the bacteria).

5.4.3 Antimycobacterial

Antimycobacterial agents are the drugs used in the treatment of infections caused by mycobacteria. Mycobacteria are Gram-positive acid fast bacilli. Antituberculous and antilepral agents are Antimycobacterial agents.

5.4.4 Antifungal

Antifungal agents are the drugs used against the infection caused by fungi they can be either fungistatics or fungicides. Fungi are parasites.

5.4.5 Anti-inflammatory

Anti-inflammatory drugs **modify the inflammatory response** to diseases but are **not curative** and do not remove the underlying cause of the disease. Any ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation and not interfere with the normal inflammatory response which is a part of the body's vital defense mechanisms to invading micro-organisms.

5.4.6 Anti-rheumatic Drugs

Rheumatic diseases are **inflammatory conditions** that **affect connective tissue**. They include rheumatoid arthritis, spondylitis, gout, rheumatic fever systemic lupus erythematosus, and psoriasis and polyarteritis nodosa. Anti-rheumatic drugs primarily act on the inflammatory process. Drugs modify the inflammatory response to disease but are not curative and do not remove underlying cause of the disease, An ideal anti-inflammatory drug affects uncontrolled excessive inflammation, relieves pain, swelling. Aspirin, salicylates, phenylbutazone and oxyphenbutazone, indomethacin, mefenamic acid and gold compounds are some of the anti-rheumatic drugs moderately effective with minimum side effects. Other steroids and non-steroidal drugs have diverse chemical structures producing similar biochemical antiflmmatory processes and thus they are less or more effective as anti-rheumatic drug.

5.4.7 CNS drugs

Central nervous system (CNS) composed of complex network of sub units which act as conducting pathways between peripheral nervous system, receptors and effectors.

These drugs produce depressing effect on the central nervous system as their principal pharmacological action. These include general anesthetics, hypnotics, sedatives and tranquilizers. Anesthetics, hypnotics and sedatives produce depressing effect on central

nervous system in the decreasing order. Sedatives exert milder depression on central nervous system. Hypnotics induce sleep while anesthetics induce different degrees of depression finally leading to unconsciousness. Tranquilizers are the central nervous system selective depressants having skelelal muscle relaxant properties. Central nervous system is subjected to **depression by these drugs** in the **following order** depending upon dosage.

Sedation ⇌ Hypnosis ⇌ Anesthesia ⇌ Coma⟶ Death

5.4.8 Cardio-Vascular drugs

These are the drugs which influence hearts mechanism (either stimulate or depress the heart by different mechanism).They produce direct action on the heart or on the other parts of the vascular (blood vessels) system these drugs affect heart muscles.

5.4.9 Anti-viral drugs

They are selective inhibitors of one or more unique steps of the replicate cycle of viruses. They improve antibody formation and activity. They are selectively active against either RNA-containing or DNA containing viruses.

5.4.10 Anticancer drugs

Cancer is a form of **abnormal development**, transforming normal cells into cancerous cells. It is a **tumour** which means an **unusual amount of growth** or **enlargement** of a **tissue** due to **unlimited** and **uncontrolled repeated divisions** of **cells**. Anticancer drugs are used for the treatment of cancer in combination; they interfere with cell division. Various alkylating agents react with DNA leading to cross-linking, dipurination and scission; these agents interfere with enzymes required for biosynthesis of nicotinamide adenine dinucleotide (NAD), since the NAD content of tumor cell gets diminished after the treatment with alkylating agents.

5.4.11 Diagnostic Agents

Diagnostic agents are substances used to defect abnormal conditions and functioning of the body. Radiopaques are diagnostic aids; they are the substances that absorb x-rays and consequently produce a shadow of positive contrast in soft tissue structures (Urinary bladder, gall bladder, stomach) during roentgenographic examination, on the other hand, air produces a shadow negative contrast.

Abnormalities or pathological disfunction of several organs of the body are diagnosed by various agents like agents for liver function test, kidney function lest.

5.4.12 Vitamins

They are comparatively simple **organic compounds** which are required in small quantities by animals for their **maintenance** and **normal growth** of **life**. Except vitamin D, animal body cannot synthesize any other vitamin. They are mainly supplied by the food we take. If the diet lacks any one or more vitamins, a deficiency disease results. There are about 25 vitamins known. Of these, vitamins B and C are water soluble while vitamin A, D, E and K are fat soluble.

5.4.13 Hormones

They are **chemical substances produced in** certain specific parts of the body called **ductless glands** also known as endocrine glands. These glands deliver the hormones in small amount directly into the blood stream. These substances then exert physiological effect at a site of action which is remote from its origin. They are required in small amount and are specific in their action. A deficiency of a particular hormone leads to a specific disease which can be cured by the administration of that hormone.

5.5 CLASSIFICATION OF DRUGS

Drugs can be classified according to various criteria. Usually, they may be classified in the following two ways:

- On the basis of their chemical structures
- On the basis of their therapeutic actions

5.5.1 On the basis of their chemical structure

This classification was extensively used some years ago and it is still used by some authors. Following the classification, drugs may come in one or more of these categories such as acetals, acids, alcohols, amides, amidines, amines, amino acids, amino alcohols, amino ethers, amino ketones, ammonium compounds, azo compounds, enols, esters, ethers,

glycosides, guanidines, halogenated compounds, hydrocarbons, ketones, lactams, lactones, mustards, nitro compounds, nitroso compounds, organominerals, phenols, quinones, semi-carbazides, semicarbazones, stilbenes, sulfonamides, sulfones, thiols, thioamides, thioureas, ureas, ureides, urethans.

5.5.2 On the basis of their therapeutic actions

Whenever the classification of drugs is done on the basis of their chemical structure, there occurs splitting up of groups of drugs which have the same physiological action. Also, the chemical structures of drugs represent such diverse structures that very little knowledge is obtained by placing them in special chemical categories. Whenever, on the other hand, the classification of drugs is done on the basis of their therapeutic action, this will tend to obscure their chemical resemblances and, thus, it would be difficult to give description of chemistry of various groups of drugs

Moreover chemical classification is only suitable for studying their chemical properties, synthesis and soon but not their therapeutic action. On the other hand, a rigid therapeutic classification would render it difficult to give the description of chemistry of various groups of drugs.

By keeping the various limitations of the two systems of classification of drugs in view, a compromise between the two ways is struck. The drugs are first divided accordance to their therapeutic actions and then sub-divided according to their chemical structures.

According to their therapeutic actions, the drugs are classified into following broad types:

5.5.2.1 CNS or Psycho-pharmacological Agents

These are the drugs which are acting, on the central nervous system. The central nervous system in man consists of the brain and the spinal cord and is able to control the thought process, emotions, senses and motor functions. Drugs in this category, the psychotropics, include anti-depressants, antipsychotics, anxiolytics and psychomimetics, all of which affect mood or mental functioning, CNS drugs also include (a) anti-convulsants used for the treatment of epilepsy, a major convulsive disease, (b) Sedative-hypnotics, which are used to sleep disorders (c)amalgesics for the control of pain and (d)anti-parkinsonian agents, used for the treatment of Parkinson's disease which is a major motor disorder.

5.5.2.2 Pharmacodynamics Agents

These are drugs which affect the normal dynamic process of the body, especially the blood circulation. This group includes anti-arrhythmics, anti-anginals, vasodilators, anti-hypertensives and anti-thromobotics, all of which in some way affect the heart or blood circulation. This category also includes drugs used for the treatment of a wide variety of allergic diseases and drugs which affect the gastro-intestinal system.

5.5.2.3 Chemotherapeutic Agents

These are an extremely important class of compounds which are selectively more toxic for invading organisms than for the host and include the antibiatics, antineoplastics, antivirals and antifungals.

5.5.2.4 Metabolic Diseases and Endocrine Function

This category includes a miscellany of agents not conviently classified in the other groups. Hence the group comprises drugs for treatment of inflammation, rheumatoid arthritis, diabetes, disorders of lipid metabolism, atherosclerosis, as well as sex hormones and peptide hormones.

According to their therapeutic actions, the drugs may be classified into the following types

5.5.2.5 Drugs acting on the central nervous system

Drugs acting on the central nervous system can either depress or stimulate its function. These drugs are usually divided into three broad classes:

- **Nonselective central nervous system depressants**: general anesthetics, hypnotics and sedatives, narcotic analgesics, antipyretic and anti-rheumatics analgesics.
- **Selective modifiers of central nervous system**: anticonvulsants, antitussives, psychotherapeutic agents, central intraneural blocking agents.
- Central nervous system stimulants

5.5.2.6 Drugs stimulating or blocking the peripheral nervous system

Drugs acting on the peripheral nervous system can either stimulate it or block it. With the exception of local anesthetics, all these drugs act by altering the transmission of impulses between synapses or between neuroeffector junctions. They comprise the following classes of drugs,

- Cholinergic and anticholinergic agents.
- Adrenergic stimulants, adrenergic blocking agents, and inhibitors of catecholamine biosynthesis and metabolism
- Histamine and antihistamine agents
- Local anesthetics

5.5.2.7 Drugs acting on the cardiovascular hematopoietic and renal systems

This group includes drugs that affect cardiovascular function as well as those that act on blood vassels and the renal system. Cardiovascular agents include cordiotonic, antiarrhythmic, antihypertensive, vasodilator, and hypocholestermic agents.

Drugs acting on the blood are called hematological agents. They are comprised of antianaemics, coagulants, anticoagulants and plasma expanders.

Agents that affect the renal system are called diuretics.

5.5.2.8 Chemotherapeutic drugs

Chemotherapeutic agents are drugs used in the treatment of infectious diseases. These diseases are caused by certain species of metazoa, protozoa, fungi, bacteria, ricketiasa and viruses. Drugs active on these pathogenic agents may be further divided into the following types;

- Organometallic Compounds
- Anthelmintic Agents
- Anti-malarial Agents
- Antiprotozoal Agents
- Antiseptic, Antifungal, and Antibacterial Agents
- Sulfonamides
- Antituberculous and Antilepral Agents
- Antibiotics
- Antineoplastic Agents
- Antiviral Agents

The term chemotherapy, which literally means "**chemical therapy**" or "**chemical treatment**," was coined in 1913 by Paul Ehrlich, the father of modern chemotherapy. He uttered the famous phrase: Corpora non agunt nisi fixata (Drugs do not act unless they bind). Ehrlich's effort was directed toward the discovery of the "**magic bullet**," that is a chemical substance with selective action on the parasite but devoid of toxic effects to the host.

Ehrlich defined chemotherapy as the use of drugs to injure an Invading organism without causing injury to the host. According to Ehrlich, therefore, chemotherapeutic agents are chemical substances with high parasitotropism and low or no organotropism. In other words, they have selective toxicity, being harmful as much as possible to the invading organism but innocuous to the host.

Although some authors impart to chemotherapy a broader meaning, such as- treatment of any disease by chemicals, including infectious and noninfectious diseases, such as psychic disorders, most authors adhere to Ehrlich's definition.

Differences between chemotherapy and pharmacodynamic agent

- Chemotherapeutic agents find use in the treatment and cure of infectious disease; pharmacodynamic agents are used for relief and correction of abnormal functions.
- Chemotherapeutic agents usually exert an irreversible action, by attaching strongly, sometimes through a covalent bond, to special moieties of macromolecules of the invading organism; pharmacodynamic agents should preferably produce reversible results, by forming weak bonds with pharmacological receptors.
- In chemotherapeutic agents the all-or-nothing effect has been unobjectionable, whereas pharmacodynamic agents are expected to give a graded response, according to the doses administered.

- Potential chemotherapeutic agents are often easily screened, because in many cases it is very simple to isolate the invading organism and study it separately; pharmacodynamic agents have been found to be more difficult to test, because it is not possible as yet to isolate receptor molecules.

Some chemotherapeutic agents may have one or both of the following effects

- static, when they inhibit further growth or multiplication of the invading organism or cell
- Cidal, when they kill or destroy it. For instance, we have both bacteriostatic and bactericidal agents.

Static or cidal effects depend on several factors, such as concentration of the drug, pH, temperature, duration of action, metabolic phase of the invader, presence of interfering substance. Thus drugs with static effects may exert cidal effects if the doses are increased.

The ideal chemotherapeutic agent is considered to be one with selective toxicity to the parasite and innocuity to the host. As no such an agent exists and very likely never will be developed or found, the relative efficiency and safety of chemotherapeutic agents has-been indicated by the so-called chemotherapeutic index, which may be expressed by the relationship

$$\text{Chemotherapeutic index} = \frac{\text{maximum tolerated dose by the host}}{\text{Minimum curative dose}}$$

The greater this index, the better the chemotherapeutic agent because of its greater safety to the patient.

5.6 RELATION OF CHEMICAL STRUCTURE AND CHEMICAL ACTIVITY

5.6.1 Introduction

During the19th century, a number of natural products were isolated and attempts were made to correlate their chemical structures with their physiological activity. From this study; it was concluded that the physiological activity of a compound is associated with a particular structural unit or group called pharmacophore group. On this basis it was found that if the pharmacophore, group disappeared then the compound was found to lose its activity. On the other hand it was observed that if pharmacophore group is introduced in to some other compound, then this compound; was found to lose its activity.

If the compound having a particular pharmacophoric group has been found to be toxic, then this group would be somewhat modified by using simple reactions to yield a compound which is physiologically more active or is less toxic or both. There, are no bard and fast rules connecting chemical structure and physiological activity but still some physiological effect has been found to be associated with a particular structural unit or group. The following gives a short account of physiological effects exerted by a given compound due to the presence of a certain functional group.

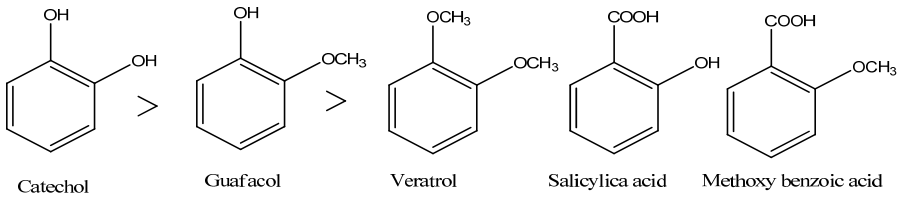
5.6.2 Effect of alkyl group

Whenever **active hydrogen** of a drug is **substituted** by an **alkyl group**, the following observations are to be noted:

(a) In some compounds, the **biological activity** is **decreased on alkylation** i.e. the biological activity of the alkylated compound is decreased to that of the non-alkylated. For example, the convulsive properties of ammonia are decreased by introducing methyl groups in place of its hydrogen atoms, i.e., trimethylamine becomes free from all these effects.

$HCN \longrightarrow RCN$, $ArOH \longrightarrow ArOR$, $RNH_2 \longrightarrow RNHR$

Similarly the convulsive properties of aniline are diminished when the hydrogen atoms of aniline are replaced by alkyl groups. Similarly, the other examples in which the replacement of hydrogen atoms by alkyl groups diminished their biological activity are as follows:

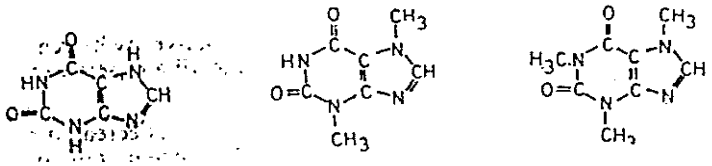


Catechol Guafacol Veratrol Salicylica acid Methoxy benzoic acid

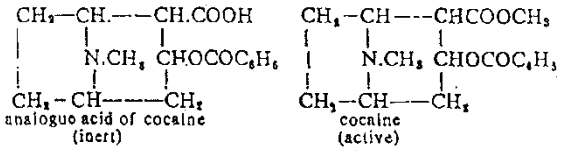
(b) In some compounds, the **toxicity is increased on alkylation**.

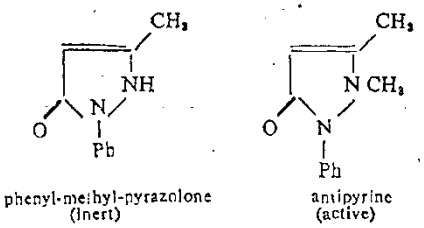
For example

- Some simple alkylamines have been found to be more toxic than ammonia
- Ethers(R—O—R) have been found to be more toxic than alcohols (R—O—H)
- Resorcinol dimethylether has been found to have much more toxicity than resorcinol
- Theobromine (N-dimethyl derivative of xanthine), and caffeine (N-tiimethyl derivative of xanthine) have been found to be much more toxic than the parent compound, xanthine.



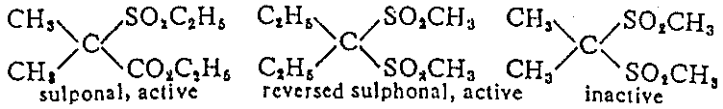
(c) In some compounds, the alkylation of a carboxyl, hydroxyl and amino group cause the full appearance of certain masked properties. For example, cocaine is a strong anesthetic while its analogue acid is inert; antipyrine is a strong antipyretic while its analogue having only one methyl group is inert.



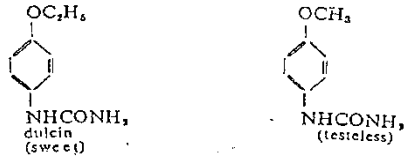


The **size of alkyl group** also shows **marked effect** on the **pharmacological activity**, e.g., the ethyl group has more marked influence as compared to that of methyl group. It is evident from the following examples:

- Diethyl ketone is a stronger hypnotic than acetone.
- When methyl group of acetophenone (hypnone) $C_6H_5COCH_3$ is replaced by ethyl group, the resulting compound $C_6H_5COC_2H_5$ has more hypnotic activity.
- Sulphones form the most important example of the comparative influence of methyl and ethyl groups.



- Dulcin having an ethyl group is about 200 times as sweet as its methyl analogue which is tasteless.



- It was shown by Ehrlich and Micbaelis that certain dyes having NEt_2 grouping possess the property of dyeing the nerve fiber while the corresponding dyes having NMe_2, group do not show this property.

5.6.3 Effect of hydroxyl group

The introduction of **hydroxyl group** into an **aliphatic compound weakens** its physiological action. This weakening has been found roughly proportional to the number of hydroxyl groups introduced into the aliphatic compound. It is evident from the following examples:

- n-Propanol is more active than glycerol

- Hexanol is more active than sorbitol
- Butyraldehyde is more active than β-hydroxy derivative (aldol) etc

Sometimes the presence of a hydroxy group makes the **compound to lose** its particular physiological activity. **For example**, hydroxycaffeine has none of the physiological activity present in caffeine. Similarly, the toxic hexaldehyde gives medicinally, inert glucose on the introduction of the hydroxyl groups.

The **isomeric alcohols** having the same number of carbon atoms show a **drop of activity** from the primary to secondary to tertiary. For example, the phenol co-efficient of 1-propahol against Staph. aures is 0.082 as compared to that of 0.054 for 2-propanol. In homologous series, generally the members having side chains are more active.

The **physiological activity** is generally **decreased** by **etherification, esterification** and the conditions unfavourable to ester hydrolysis. It has been proved beyond doubt that the hydroxyl group itself, in such compounds, does not have physiological action of its own but it simply anchors the molecule on a reactive position of cell chemical.

In the case of **aromatic compound**, the **introduction** of a **hydroxyl group increases** the physiological activity of the compound. This is **completely reverse** to that in the **aliphatic compounds**: **E.g.** phenol is more toxic and a strong antiseptic than benzene; salicylic acid is not only a stronger antifungal agent but is also an anti-rheumatic agent, a property missing in the inert parent compound, the benzoic acid. Introduction of **more hydroxyl groups** in **aromatic nucleus increases** the **toxicity**. For example, resorcinol and pyrogyllol are more toxic than phenol.

5.6.4 Effect of aldehyde and ketone groups

Aldehydes are **more reactive** than **ketones** and thus also **exhibit** a **more** intense **biological activity**. Formaldehyde, the simplest aldehyde, has a strong antiseptic property and a hardening effect on the tissues, a property for which it is used by taxidermist. The higher members have the combined property of the aldehydic and alkyl groups. The **introduction** of **hydroxyl groups** in the **aldehyde molecule decreases** the physiological activity of the compound which may even cause the compound to be medically inert, viz., glucose. However, on the whole the physiological effect produced by aldehydes cannot be generalised.

In general, the pharmacological properties of **ketones** have been found to be **similar to** that of the **corresponding secondary alcohols**, i.e., ketones, in general, possess narcotic action. In aliphatic ketones, due to the presence of alkyl groups, the hypnotic action is fairly well marked but the mixed ketone, acetophenone $C_6H_5COCH_3$ is a strong hypnotic (used under the name hypnone*).* aβ-unsaturated ketones are found to possess diuretic activity.

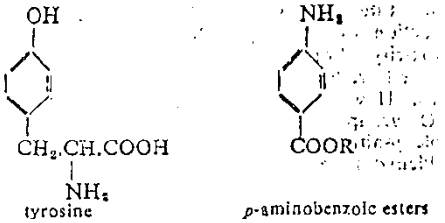
5.6.5 Effect of acidic groups

The introduction of an **acidic group** such as —SO_3H or —COOH in a molecule either **decreases** or completely destroys the physiological activity of the parent compound. For example, phenol is poisonous but benzene sulphonic acid is harmless. From this it may appear that this is because of the disappearance of OH group.

However, the introduction of acidic groups without altering the active or anchoring groups also makes compound less toxic. It is evident from, the following examples:

- Nitro benzene is poisonous but nitro benzoic acids are harmless.
- Amines are toxic but amino acids are food-stuffs.
- Aniline is toxic but m-amino benzoic acid is harmless.
- Martius yellow (dinitro naphthol) is markedly toxic but its sulphonic acid (naphthol yellow S) is harmless.

However, the physiological properties of the compounds which have disappeared due to the introduction of acidic, groups can be restored by esterification For example, tyrosine, a phenolic amino acid, is harmless while its ethyl ester is poisonous.

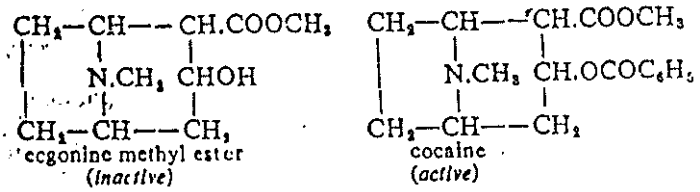


tyrosine *p*-aminobenzoic esters

Similarly, p-amino benzoic acid has no anesthetic property but its alkyl esters are used as local anesthetics.

The acylation of basic compounds by means of organic acids reduces the basicity and physiological action of the compounds.

The benzoylation has been found to increase the physiological activity of the various compounds. For example, ecgonine methyl ester is inactive while its benzoyl derivative, cocaine, is an important local anesthetic.



5.6.6 Effect of halogens

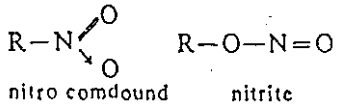
The **introduction** of **negative halogens**, i.e. when the halogen is present in non-conjugated positions, has been found to **increase** the useful as well as the toxic properties but at different rates. However, the halogenation increases the toxicity only to a limited extent but increases the useful properties appreciably. Hence halogenation is used for increasing activity and widening the margin of safety in the given series.

On the other hand, the **introduction** of **positive halogens** as in acid halides, a-halogenocarbonyl compounds **decreases** the toxicity of the compounds. Compounds having available halogens, such as chloramines are strongly antiseptic, depending upon the percentage of hypohalous acid liberated on hydrolysis.

Among halogens Cl, Br and I, **hypnotic properties** generally **decrease with increase** in **atomic weight** but the **antiseptic properties increase**. This can be seen from the comparison of hypnotic and antiseptic properties of $CHCl_3$, $CHBr_3$, and CHI_3 in which the hypnotic activity decreases whereas antiseptic activity increases from chloroform to iodoform. It is to be noted that fluorine compounds are comparatively much less physiologically active than the corresponding other halogens. The less activity of fluorinated compounds may be due to their stability.

5.6.7 Effect of nitro (NO_2) and nitrite (ONO) group

The **introduction** of a **nitro group** into **aromatic compounds increases** their toxicity. For example, nitrobenzene, nitronaphthol and nitro-thiophene have been found to be more toxic than the parent hydrocarbons. However, if a **readily oxidisable group** such as —CH_3 or — CHO group is introduced, then the toxicity **decreases**. For example, p-nitrotoluene is less poisonous than nitrobenzene and also nitroaldehydes are somewhat little poisonous.



Nitrite group, which is isomeric with nitro group, differs in their action. For example, aliphatic nitrites have dilating effect on blood vessels whereas nitro compounds have no action. Thus, **aliphatic nitrites** are used to **lower blood pressure**. The strength of this effect increases from methyl nitrite to amyl nitrite. The secondary and tertiary nitrites are easily hydrolyzed to alcohol and nitrites. Therefore, they are more powerful than the corresponding primary nitrites.

5.6.8 Effect of amino group

In general, the **amino group** is **toxic**. Successive alkylation of the amino group decreases toxicity. In general, the acylation of amino group decreases the physiological activity, e.g., aniline is toxic while acetanilide is used as a febrifuge.

Sulphonation and carboxylation decrease the physiological effect of the amino compounds, e.g., aniline is poisonous while p-amino benzoic acid (PABH) is actually a vitamin of B group. The **introduction** of a **second amino group increases** the toxicity. For example, all the three phenylenediamines are more poisonous than aniline. It is to be remembered that aromatic amines and hydrazines are used as antipyretics and analgesics.

5.6.9 Effect of nitrite (—CN) group

The parent compound of nitrile group is HCN which is a well known, strong poison. The introduction of nitrile group may give rise to two series of compounds, the **nitriles RCN** and **isonitriles RNC, both** are **poisonous**.

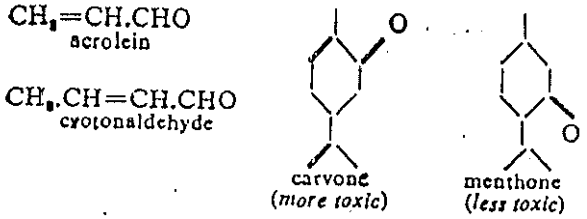
Nitriles produce coma. In aliphatic series, the lower nitrites have been found to be more poisonous than the higher nitriles.

Isonitriles are also very poisonous. They paralyze the respiratory systems.

The cyanide ion in some inorganic compounds also exerts more poisonous effect. For example, potassium thiocyanate is a weak poison and sodium nitroprusside, $Na_2Fe(CN)_5NO$ is a strong poison which causes death. However, the cyanide ion in the sodium ferrocyanide $Na_4Fe(CN)_6$ does not have any physiological action.

5.6.10 Effect of unsaturation

In general, the **unsaturated compounds** have been found to be **more toxic** than their **corresponding saturated compounds**. For example, propanol-1 $CH_3CH_2CH_2OH$ has mild narcotic property but is non-poisonous while allyl alcohol $CH_2=CHCH_2OH$ has strong poisonous properties. Also, unsaturated compounds such as acrolein, crotonaldehyde and carvone have been found to be more toxic than that of the corresponding saturated compounds.



It is to be noted that the toxicity of a compound increases with unsaturation. Unsaturation has also been found to produce toxicity in the compounds other than carbon. For example, trivalent arsenic compounds have been found to be more toxic than those of quinquevalent arsenic. Also, mustard gas $(ClCH_2CH_2)_2S$ is poisonous which on oxidation is converted into almost harmless and non-toxic substance, the sulphone $(ClCH_2CH_2)_2SO_2$ (oxidation increases the valency of sulphur).

5.6.11 Effect of Isomerism

5.6.11.1 Structural isomerism

Structural isomers often **show marked differences** in their physiological properties. This can be seen in ortho, meta and para derivative in the aromatic series. For example, o-hydroxybenzoic acid is physiological active while both p- and m- isomers are inactive. Similarly, it can be explained that ordinary cocaine is a local anesthetic while a-cocaine does not have this property. p-Aminobenzene sulphonic acid is an active drug whereas its two other isomers are inactive.

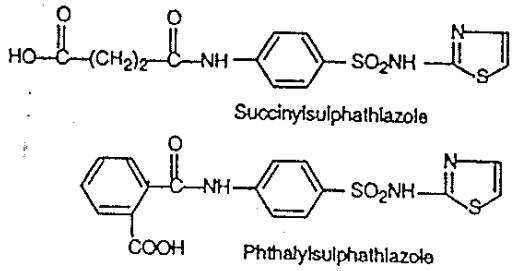
5.6.11.2 Stereoisomerism

Both geometrical and optical isomers show different physiological activity, **e.g**. maleic acid is poisonous while fumaric acid is harmless. (—)Adranaline is about 12 times as active as the (+) form. Similarly, (—) nicotine is twice as active as (+) form.

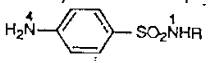
5.7 SULPHA DRUGS

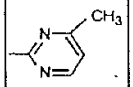
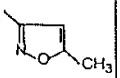
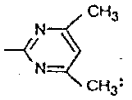
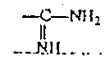
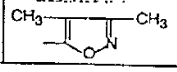
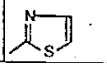
Table 1 lists the commonly used sulpha drugs (also called sulphonamides), together with their structures and names. For naming them, the sulphonamide nitrogen is numbered N^1 and the amino nitrogen is numbered N^4.

Occasionally, there are sulphonamides in which N^4 substituted by acyl group. For example,



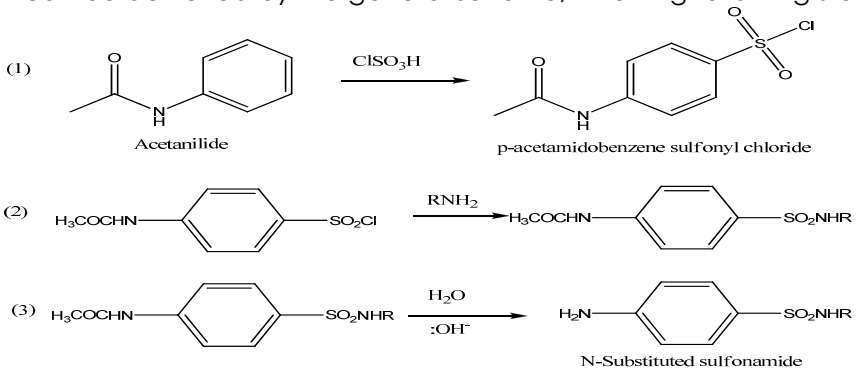
Tabe 1: Some commonly used Sulpha drugs



S.N.	Drug	R	S.N.	Drug	R
1.	Sulphanilamide	—H			
2.	Sulphacetamide	—$COCH_3$	7.	Sulphamerazine	
3.	Sulphadiazine		8.	Sulphamethoxazole	
4.	Sulphadimidine		9.	Sulphapyridine	
5.	Sulphaguanidine				
6.	Sulphisoxazole		10.	Sulphathiazole	

5.7.1 Synthesis of N^1-Substituted sulphonamides

It can be achieved by the general scheme, involving following steps:



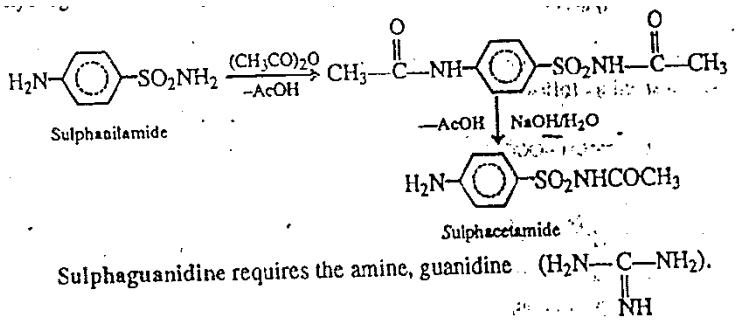
Remember that in step (iii)—CONH group, that is hydrolyzed more readily than —SO_2NH group.

The step (ii) in the above scheme requires different RNH_2 for each sulphonamide. The synthesis of important sulphonamides is outlined below.

For sulphanlamide, simple ammonia *is needed in step* (ii).

5.7.2 Sulphacetamide

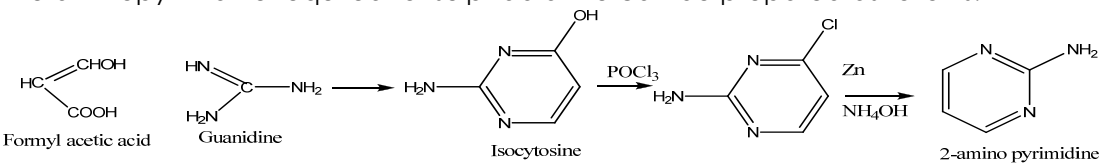
Which does not require an amine (RNH_2) can be synthesized from sulphanilamide itself by acetylatlon of both N^1 and N^4 hydrogen followed by selective alkaline hydrolysis of N^4 acetyl group.



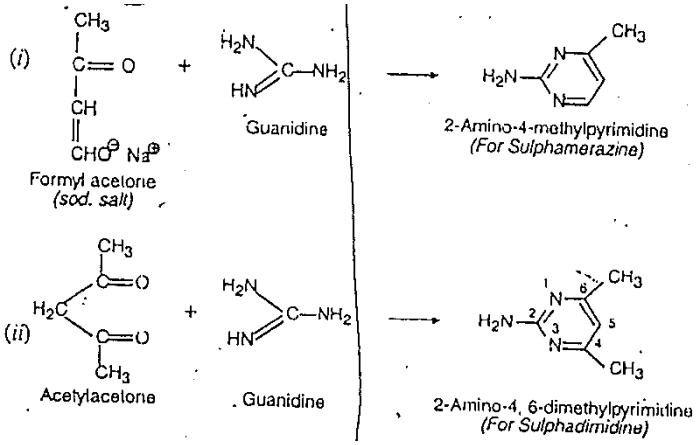
Sulphaguanidine requires the amine, guanidine $(H_2N-C(=NH)-NH_2)$.

The 2-aminopyridine required for sulpha pyridine can be prepared from pyridine by reaction with sodamide (chichibabin reaction)

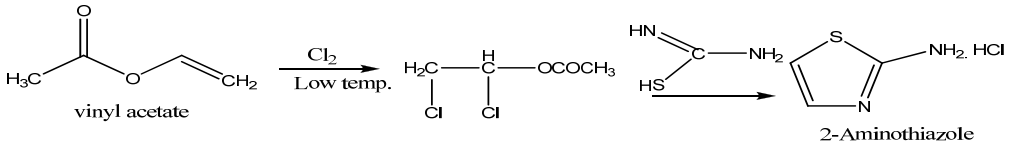
The aminopyrimidine required for sulphadiazine can be prepared as follows:



The aminopyrimidines required for sulphamerazine and sulphadimidine can be synthesized as follows



The amine required for sulphathiazole is 2- aminothiazole. It can be synthesized as follow:



Sulphisoxazole and sulfamethoxazole require 3, 4-dimeihyl-5-aminoisoxdzole and 3-amino-5-methylisoxazole respectively as the coupling amines in step (ii).

5.7.3 Synthesis of Succinylsulphathiazole and phthalylsulphathiazole

These N'- substituted sulphonamides can be prepared from sulphathiazole as per following scheme.

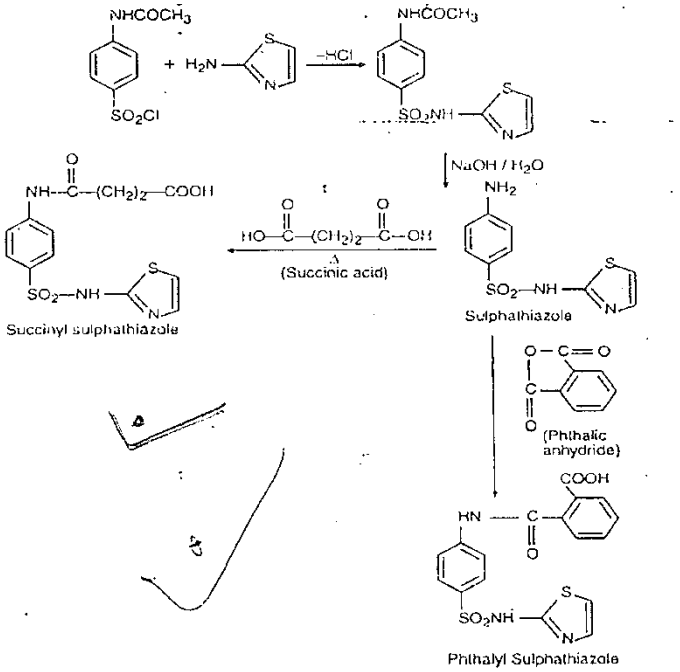
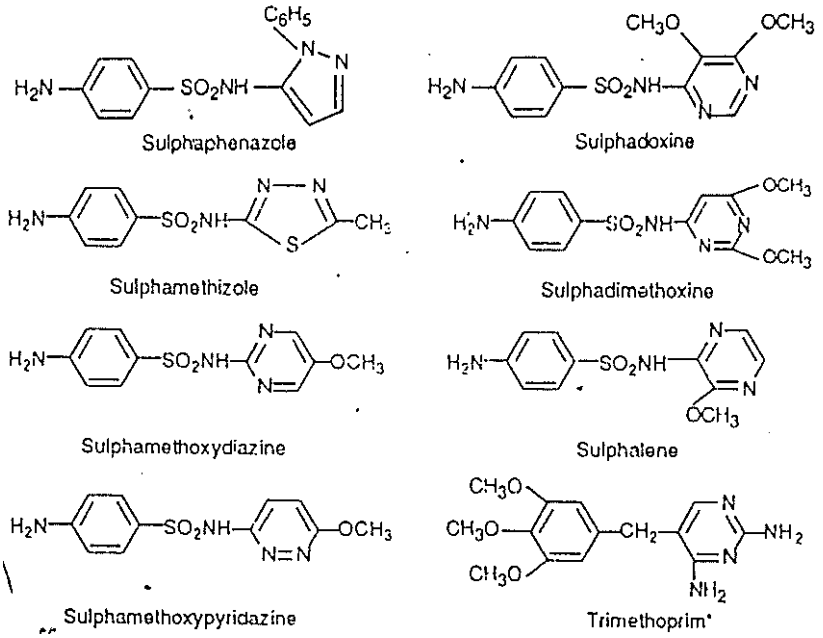


Fig. 1. Synthesis of sulphathiazole, succinylsulphathiazole and phthalylsulphathiazole.

5.7.4 Some additional sulphonamides

Chart 1 lists some additional sulphonamides which have assumed importance in recent years.

Chart 1. Some recent sulphonamides



5.7.5 Uses

The sulphonamides are the first **effective chemotherapeutic agents** to have been employed for the **prevention** and **cure** of **bacterial infections** in man. Those derived from pyrimidine (1, 3-diazine) have been most successful in the clinical world. Although sulphonamides have been **largely replaced** by **antibiotics** in the treatment of infections, they are **still used** where **patients are intolerant of antibiotics**. The individual sulphonamides do not differ much in their activity against specific microorganisms. However, they differ from one another in their degree of absorption; their diffusion to the body tissues and their rate of elimination from the body. Sulphadiazine*(pyrimai)*, sulphadimidine, sulphapyridine, sulphisoxazole, sulphamethiazole and sulphathiazole for example, at readily absorbed.

Sulphlsoxazole (sulphafurazole), suiphamethizole, sulphamethoxazole and sulphaphenazole are used in the **treatment of infections of urinary tract**.

Sulphapyridine is useful in the treatment of a certain type of **dermatitis**.

Mixed with trimethoprim (see Chart 1), sulphamethoxazole is used in a wider range of **infections**, besides **urinary tract infections** and **lower respiratory tract infections**.

Sulphadoxime, sulphadimethoxide and sulphamethoxydiazine, stilphamethoxy-pridazine and sulphalene, commonly called long-acting sulphonamides, are given once a day or even longer in the case, of **chronic infections**. They are particularly effective in urinary tract infections.

Sulphadoxine has been used also in the treatment of **leprosy**.

Succinylsulphathiazole and phthatylsulphathiazole are relatively poorly absorbed and are used in the treatment of bacillary dysentry and as adjuncts in the treatment of **ulcerative colitis**. Phthalylsulphathiazole is, however, preferred.

Sulphacetamide sodium, in the form of the popular brands Albucid and Loculaq, are applied locally in **infections of the eyes**.

Sulphaguanidine, which is poorly absorbed by the intestinal mucosa, has been used in the treatment of **bacillary dysentery**. It can be given in large doses without the development of high blood levels and toxic side effects.

Sulphadiazine is a drug of choice in a number of infections including **pneumococcal, meningococcal** and **H. influenzae**. It has fewer toxic reactions.

Sulphathiazole is more patent than sulphapyridine in the treatment of **streptococcal, staphylococcal, pneumococcal** and **gonococcal infections**, and is generally the drug of choice in the treatment of these infections.

5.8 ANTIPYRETICS AND ANALGESICS

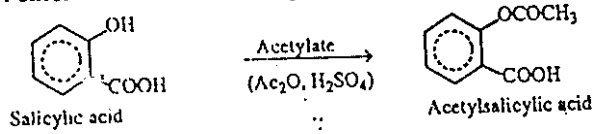
Drugs used to **lower body temperatures** in feverish conditions are called **antipyretics**. **Analgesics** are the drugs used to **relieve pain** in various conditions of health **without loss of consciousness**. The antipyretic action and the analgesic action are usually found together in the same drug. Many synthetic analgesics and antipyretics are known today common being aspirin, phenacetin, paracetamol, phenylbutazone, etc. Some representative analgesics antipyretics are described below :

5.8.1 Aspirin (Aspro, Empirin), acetylsalicylic acid

Among salicylic acid derivatives, this is the most important synthetic analgesic, antipyretic, and anti-inflammatory agent.

5.8.1.1Synthesis

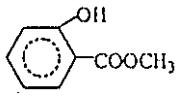
It consists in acetylating salicylic acid with acetic anhydride or acetyl chloride.



It is a common remedy for the relief of headache, muscular pain and toothache. However, its use in children is not recommended. The toxic-side-effect of 'aspirin-therapy' is gastric irritation leading to ulceration. Therefore, it should not be taken on an empty stomach. It is used orally alone or in conjunction with caffeine or codeine (methyl ether of morphine). It is used widely in the treatment of acute and chronic states of rheumatism gout etc.

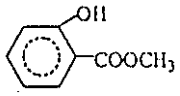
The calcium salt of aspirin, which is soluble in water, is better than simple aspirin in that it has fewer undesirable side-effects and inducts analgesia faster than aspirin. A familiar preparation of soluble aspirin is 'Disprin'. Disprin contains calcium carbonate and anhydrous citric acid besides aspirin, and this renders aspirin water soluble. Disprin relieves pain faster than aspirin.

5.8.2 Methyl salicylate (Oil of wintergreen)



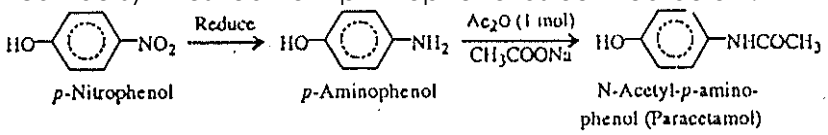
It occurs in nature and it can be made synthetically too. It is applied as such or in liniments and ointments, for the relief of pain of lumbago, sciatica and rheumatic conditions. It is also used as a flavouring agent. It is the main constituent of pain reliever 'Iodex'.

5.8.3 Paracetamol (Acetaminophen), p-Acetamido phenol, N-acetyl-p-amino phenol



5.8.3.1 Synthesis

It can be synthesized from p-nitrophenol as outlined below:

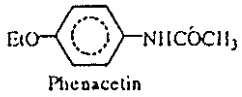


5.8.3.2 Uses

It has analgesic and antipyretic activities. It is being used as such under various trade names like Crocin, Metacin etc. It is also marketed in combination with aspirin and caffeine.

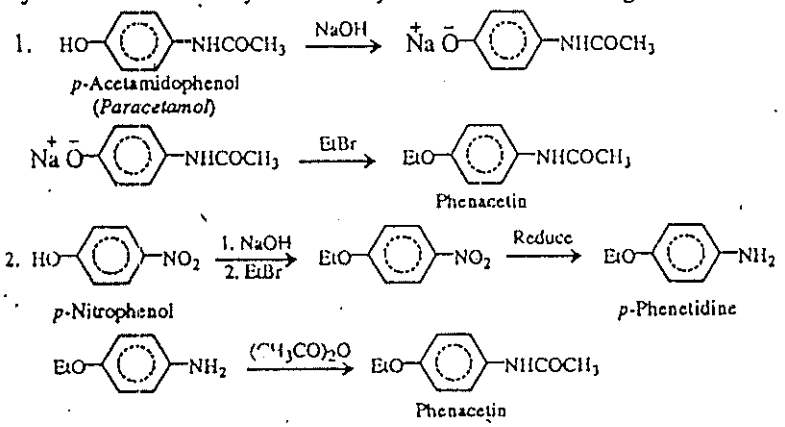
5.8.4 Phenacetin, Acetophenetidine

It is the ethyl ether of paracetamol



5.8.4.1 Synthesis

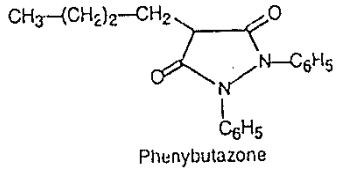
It can be synthesized by either of the following schemes:



5.8.4.2 Uses

It has been widely used as an analgesic and an antipyretic, usually in combination with aspirin, caffeine and codeine. In recent years, it has been found to be somewhat toxic in nature. It may damage kidneys if used over long periods.

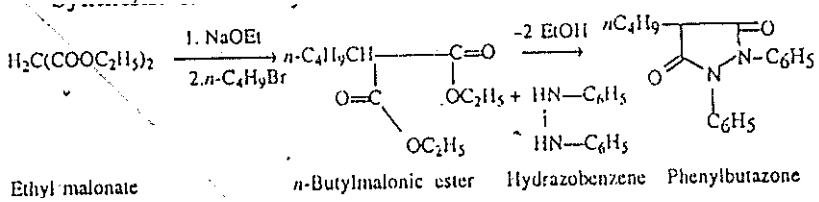
5.8.5 Phenylbutazone (Butazolidine), 4-n-Butyl-1, 2-diphenyl-3, 5-pyrazolidinedione



It is commonly used as an anti-arthritic and anti-inflammatory agent. Since it has many undesirable side-effects also, it should be used under strict supervision of a doctor.

5.8.5.1 Synthesis

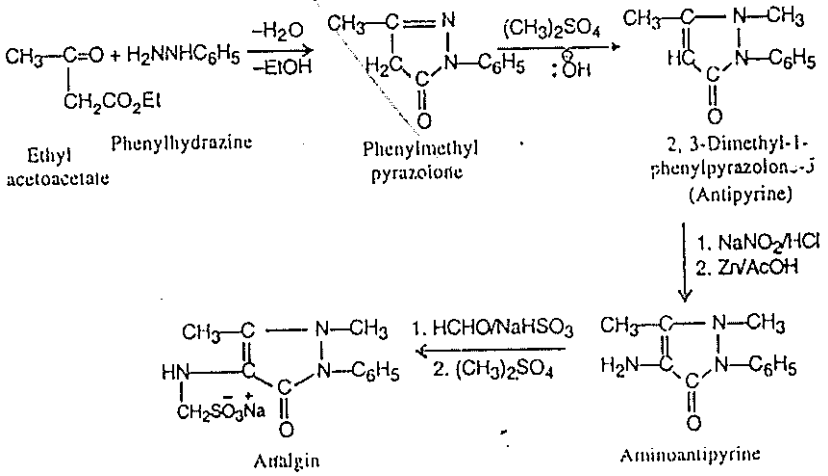
It can be synthesized from malonic ester as outlined below:



5.8.6 Analgin (Metamezole) Sodium 2,3-dimethyl-1-phenyl-5-pyrazolone-4-yl-N-methyl amino methane sulphonate

5.8.6.1 Synthesis

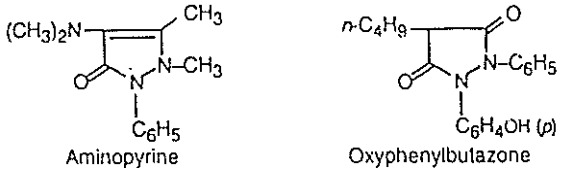
It can be prepared from ethyl aceto acetate as outlined below



5.8.6.2 Uses

It is widely used for its analgesic and antipyretic properties.

5.8.7 Some additional antipyretics and analgesics



Aminopyrine is used as an antipyretic *and* analgesic, but is slower in action. However**,** it seems to be much more effective in rheumatic fever.

Oxyphenyl butazone, sold under the trade name Tendril is a metabolite of phenylbutazone, commonly used as an antiarthritic andanti-inflammatory agent.

5.9 ANTIPYRETICS AND ANALGESICS

An **antipyretic** is a drug which is responsible for **lowering the temperature** of a feverish organism to normal but has no effect on normal temperature states. On the other hand, an **analgesic** is a drug which **relieves pain** without the loss of consciousness. The diminutions of pain may be a consequence of febrifuge effect.

In the earlier days, the antipyretic compounds studied and synthesized were also found to have analgesic properties. Therefore, these two types of drugs are studied together. However, some compounds have only the antipyretic property without any analgesic action.

Analgesics are the drugs which by virtue of their action on the central nervous system decrease the sensation of pain.

5.9.1 Classification of analgesics

It can readily be made on the basis of narcosis. Thus, analgesics can be classified into the following two groups

5.9.1.1Narcotics

They produce analgesia and sleep and in high doses cause unconsciousness. They are mainly the opium alkaloids or their synthetic and semi-synthetic derivatives **e.g.,** morphine, codeine, pethidine, etc. They are very potent drugs and their chronic use leads to addiction.

5.9.1.2 Non-narcotics

These are the drugs which are not so potent and do not cause addiction. They usually produce an antipyretic effect also. Examples of non-narcotics analgesics are aspirin, analgin, etc.

5.9.2 Mode of Action of Antipyretics

In order to regulate body temperature, there should exist balance between heat production and heat loss. The central nervous system, especially the hypothalamus, plays an important role in maintaining the balance between the two. That is why the hypothalamus is known as the **'thermostat'** of the body. In cases of fever, there still exists the balance between heat loss and heat production but the thermostat is only, set at a higher level. The **antipyretic** drug **helps to reset the 'thermostat'** for **normal temperature**. Heat production is not inhibited but heat loss is increased by increased peripheral blood slow, which **increases the rate of perspiration**. This in turn causes the body to lose heat and subsequently lowers the body temperature. Antipyretics do not have any effect *on* body temperature when it is in the normal range.

5.9.3 Mode of action of analgesics

Main function of analgesics is to relieve or decrease the sensation of pain. They act by **increasing the threshold** of **pain** which may be defined as the lowest perceptible intensity of pain. The pain is induced by a stimulus and the amount of stimulus may be regarded, as a measure of the threshold of pain. If more stimuli are required, the threshold of pain is increased and if fewer stimuli are required, the threshold of pain is decreased. When analgesics are used, the pain is not decreased but only the threshold of pain is increased. Therefore, the patient does not feel the pain.

The most commonly used antipyretics-analgesics belong to the following groups.

- Pyrazolone and pyrazolidones
- Aniline derivatives
- Derivatives of p-aminophenol
- Quinoline derivatives
- Salicylic acid and its derivatives and
- Morphine and related compounds

5.10 EXERCISE

1. Define the term drug. What are the characteristic of an ideal drug on the basis of their therapeutic action — 05
2. Explain the following terms — 03
    1. Pharmacology
    2. Chemotherapeutic agents
    3. Pharmacodynamic agents
3. Write a notes on — Each carry 3 marks
    1. Uses of sulpha drugs
    2. Antipyretic and analgesic agent
    3. Routes of drug administration and dosage forms
    4. Drug toxicity
4. Classification of drugs on the basis of therapeutic action — 05
5. Write notes on relation of chemical structure and chemical activity of drugs — 04
6. Define — 05
    1. Drug binding
    2. Antimetabolite
    3. Bacteria
    4. Mutation
    5. Chemotherapy
7. Write a notes on
    1. Prodrug
    2. Molecular pharmacology
    3. Pharmacodynamic agent

5.11 FURTHER READING

Synthetic drugs by Gurdeep R. Chatwal