

Syllabus

UNIT - I General Pharmacology

(08 Hours)

- (a) Introduction to Pharmacology - Definition, Historical landmarks and scope of pharmacology, Nature and source of drugs, Essential drugs concept and routes of drug administration, Agonists, Antagonists (competitive and non-competitive), Spare receptors, Addiction, Tolerance, Dependence, Tachyphylaxis, Idiosyncrasy, Allergy.
- (b) Pharmacokinetics - Membrane transport, Absorption, Distribution, Metabolism and excretion of drugs. Enzyme induction, Enzyme inhibition, Kinetics of elimination

UNIT - II General Pharmacology

(12 Hours)

- (a) Pharmacodynamics - Principles and mechanisms of drug action. Receptor theories and classification of receptors, Regulation of receptors. Drug receptors interactions signal transduction mechanisms, G-protein-coupled receptors, ion channel receptor, Transmembrane enzyme linked receptors, Transmembrane JAK-STAT binding receptor and receptors that regulate transcription factors, Dose response relationship, Therapeutic index, Combined effects of drugs and factors modifying drug action.
- (b) Adverse drug reactions.
- (c) Drug interactions (pharmacokinetic and pharmacodynamic)
- (d) Drug discovery and clinical evaluation of new drugs - Drug discovery phase, Preclinical evaluation phase, Clinical trial phase, Phases of clinical trials and pharmacovigilance.

UNIT - III Pharmacology of Drugs Acting on Peripheral Nervous System

(10 Hours)

- (a) Organization and function of ANS.
- (b) Neurohumoral transmission, Co-transmission and classification of neurotransmitters.
- (c) Parasympathomimetics, Parasympatholytics, Sympathomimetics, Sympatholytics.
- (d) Neuromuscular blocking agents and skeletal muscle relaxants (peripheral).
- (e) Local anesthetic agents.
- (f) Drugs used in myasthenia gravis and glaucoma

UNIT - IV Pharmacology of Drugs Acting on Central Nervous System

(08 Hours)

- (a) Neurohumoral transmission in the C.N.S. special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, Serotonin, Dopamine.
- (b) General anesthetics and pre-anesthetics.
- (c) Sedatives, Hypnotics and centrally acting muscle relaxants.
- (d) Anti-epileptics
- (e) Alcohols and Disulfiram

UNIT - V Pharmacology of Drugs Acting on Central Nervous System

(07 Hours)

- (a) Psychopharmacological agents: Antipsychotics, Antidepressants, Anti-anxiety agents, Anti-manics and Hallucinogens.
- (b) Drugs used in Parkinson's disease and Alzheimer's disease.
- (c) CNS stimulants and Nootropics.
- (d) Opioid analgesics and antagonists
- (e) Drug addiction, drug abuse, Tolerance and dependence.

Contents

Unit - I

Chapter 1 : Introduction to Pharmacology

1.1 - 1.18

1.1	Introduction	1.1
1.2	Historical Landmarks in Pharmacology	1.2
1.3	Scope of Pharmacology	1.4
1.4	Branches and Divisions of Pharmacology	1.5
1.5	Sources of Drugs	1.7
1.6	Routes of Drug Administration	1.9
1.7	Agonists	1.13
1.8	Antagonists	1.14
1.9	Spare Receptors (Reserve Receptors)	1.14
1.10	Addiction	1.16
1.11	Tolerance	1.16
1.12	Dependence	1.17
1.13	Tachyphylaxis	1.17
1.14	Idiosyncrasy	1.17
1.15	Allergy	1.18
•	Questions	1.18

Chapter 2 : Pharmacokinetics

2.1 - 2.38

2.1	Introduction	2.1
2.2	Biological Membrane	2.2
2.3	Mechanism of Drug Absorption	2.2
2.3.1	Simple Diffusion	2.3
2.3.2	Filtration	2.5
2.3.3	Bulk Flow	2.5
2.4	Carrier Mediated Transport	2.6
2.4.1	Active Membrane Transport	2.6
2.4.2	Facilitated Transport	2.6
2.4.3	Endocytosis	2.6
2.5	Factors Affecting Absorption of Drugs	2.7
2.6	Distribution of Drugs	2.11
2.6.1	Factors Affecting Distribution	2.14
2.6.2	Factors Influencing the Volume of Distribution	2.19
2.7	Metabolism of Drugs	2.20
2.7.1	Factors Affecting Biotransformation	2.26
2.7.2	Prodrugs	2.30
2.8	Excretion of Drug	2.31
2.9	Kinetic Elimination of Drug	2.33
2.9.1	Factors affecting Elimination	2.36
•	Questions	2.38

Unit - II

Chapter 3 : Pharmacodynamics

3.1 - 3.30

3.1	Introduction	3.1
3.2	Principles and Mechanisms of Drug Action	3.1
3.2.1	Principles of Drug Action	3.1
3.2.2	Mechanisms of Drug Action	3.2
3.2	Receptors	3.6

3.3	Receptor Regulation	3.8
3.4	Drug Receptor Interaction	3.10
3.5	Signal Transduction	3.13
3.5.1	Signal Transducing Receptors are of Three General Classes	3.14
3.6	Types of Receptors	3.16
3.6.1	Ligand Gated Ion Channel Receptors	3.16
3.6.2	G-protein Coupled Receptors	3.17
3.6.3	Kinase Linked or Enzymatic Receptors	3.19
3.6.4	Enzyme-linked Receptors	3.20
3.7	Dose Response Relationship	3.23
3.8	Therapeutic Index	3.24
3.9	Combined Effects of Drugs	3.24
3.10	Factors Modifying Action of Drugs	3.26
•	Questions	3.30

Chapter 4 : Adverse Drug Reactions

4.1 - 4.4

4.1	Introduction	4.1
4.2	Types of Adverse Drug Reactions	4.1
4.3	ADRs: Predisposing Factors	4.3
•	Questions	4.4

Chapter 5 : Drug Interactions

5.1 - 5.6

5.1	Introduction	5.1
5.2	Drug-Drug Interaction Classification	5.2
5.3	Pharmaceutical Interactions	5.2
5.4	Pharmacological Interactions	5.2
5.5	Pharmacokinetic Interactions	5.3
5.6	Pharmacodynamic Drug Interactions	5.5
•	Questions	5.6

Chapter 6 : Drug Discovery and Clinical Evaluation of New Drugs

6.1 - 6.8

6.1	Drug Discovery and Clinical Evaluation of New Drugs	6.1
6.2	Basic Terminologies for Pharmacovigilance	6.5
•	Questions	6.8

Unit - III

Chapter 7 : Organization and Function of Autonomic Nervous System

7.1 - 7.6

7.1	Introduction	7.1
7.2	Parasympathetic Nervous System	7.6
•	Question	7.6

Chapter 8 : Neurohumoral Transmission, Co-transmission and Classification of Neurotransmitters

8.1 - 8.8

8.1	Introduction	8.1
8.2	Physiological Steps involved in Neurohumoral Transmission	8.3
8.3	Classification of Neurotransmitter	8.6
•	Questions	8.8

Chapter 9 : Parasympathomimetics	9.1 - 9.11
9.1 Introduction	9.1
9.2 Acetylcholine Receptors	9.2
9.3 Parasympathomimetics	9.6
9.3.1 Choline Esters	9.6
9.3.2 Anticholinesterase Agents	9.10
• Questions	9.12
Chapter 10 : Parasympatholytics	10.1 - 10.6
10.1 Introduction	10.1
10.2 Classification	10.1
10.3 Sources and Chemistry of Anticholinergic Drugs	10.2
• Questions	10.6
Chapter 11 : Sympathomimetics Agents	11.1 - 11.14
11.1 Sympathetic Nervous System	11.1
11.2 Adrenergic Receptor	11.5
11.2.1 Classification of Adrenergic Agents	11.7
11.2.2 Pharmacological Action	11.8
11.3 Non-Catecholamines	11.12
• Questions	11.14
Chapter 12 : Sympatholytics Agents	12.1 - 12.10
12.1 Introduction	12.1
12.2 α -receptor Antagonist	12.2
12.3 β -receptor antagonist: (β -blocker)	12.5
12.4 α and β -non-selective Antagonist	12.8
12.5 Centrally Acting Sympatholytics	12.9
12.6 Ganglion Blockers	12.10
12.7 Neuronal Blockers	12.10
• Questions	12.10
Chapter 13 : Neuromuscular Blocking Agents and Skeletal Muscle Relaxants	13.1 - 13.4
13.1 Introduction	13.1
13.2 Neuromuscular Blocking Agents	13.2
13.3 Depolarising Blocker	13.3
13.4 Centrally Acting Muscle Relaxants	13.4
• Questions	13.4
Chapter 14 : Local Anesthetic Agents	14.1 - 14.10
14.1 Introduction	14.1
14.2 Clinical Uses and Technique of Administration	14.1
14.3 Pharmacokinetics of Local Anaesthetics	14.3
14.4 The Importance of the pKa of a Local Anaesthetic Drug	14.4
14.5 The Mechanism of Action of Local Anaesthetics	14.5
• Questions	14.10
Chapter 15 : Drugs used in Myasthenia Gravis and Glaucoma	15.1 - 15.4
15.1 Myasthenia Gravis and Glaucoma	15.1
15.2 Treatment	15.2
15.3 Glaucoma	15.2
15.4 Types of Glaucoma	15.3
• Questions	15.4

Unit - IV

Chapter 16 : Neurohumoral Transmission in the CNS

16.1 - 16.10

16.1	The Basis of CNS Pharmacology	16.1
16.1.1	Glutamatergic Pathways	16.3
16.1.2	GABAergic Pathways	16.3
16.1.3	Glycine	16.4
16.1.4	Dopaminergic Pathways	16.4
16.1.5	Cholinergic Pathways	16.5
16.1.6	Serotonergic Pathways	16.6
16.1.7	Noradrenergic Pathways	16.6
16.2	Neurohumoral Transmission in the CNS	16.7
16.3	Neurotransmitters	16.8
•	Questions	16.10

Chapter 17 : General Anesthetics and Pre-anesthetics

17.1 - 17.14

17.1	General Anesthesia	17.1
17.1.1	Stages of General Anesthesia	17.2
17.1.2	Phases of Anesthesia	17.3
17.2	Classification of General Anesthetics	17.4
17.3	Mechanism of Action of General Anesthetics	17.4
17.4	Individual Anaesthetic Agents	17.5
17.5	Mode of Delivery or Administration of General Anaesthetics	17.11
17.6	Preanaesthetic Medication or Adjuvant for General Anaesthetics	17.12
•	Questions	17.14

Chapter 18 : Sedatives and Hypnotics

18.1 - 18.8

18.1	Introduction	18.1
18.2	Sleep Cycle	18.1
18.3	Classification of Hypnotics and Sedatives	18.3
18.4	Barbiturates	18.4
18.5	Barbiturate Intoxication and Overdose	18.7
•	Questions	18.8

Chapter 19 : Centrally Acting Muscle Relaxants

19.1 - 19.2

19.1	Introduction	19.1
19.2	Pharmacology of Individual Drugs	19.1
•	Questions	19.2

Chapter 20 : Anti-epileptics Drugs

20.1 - 20.10

20.1	Epileptic Seizures	20.1
20.2	Antiepileptic Drugs	20.3
•	Questions	20.10

Chapter 21 : Alcohols and Disulfiram

21.1 - 21.8

21.1	Ethyl Alcohol (Ethanol)	21.1
21.1.1	Mechanism of Action	21.2
21.1.2	Pharmacological Action	21.2
21.2	Methanol	21.7
21.3	Disulfiram	21.7
•	Questions	21.8

Unit - V

Chapter 22 : Antipsychotics Drugs	22.1 - 22.8
22.1 Introduction	22.1
22.2 Dopamine Pathways	22.1
22.3 Antipsychotic Drugs	22.3
22.4 Dopamine Receptors	22.3
22.5 Pharmacology of Chlorpromazine	22.5
• Questions	22.8
Chapter 23 : Antidepressants Drugs	23.1 - 23.6
23.1 Introduction	23.1
23.2 Antidepressants Drugs	23.2
23.2.1 Classification	23.2
23.2.2 Monoamine Oxidase Inhibitors	23.2
23.2.3 Tricyclic Antidepressants (TCAS)	23.4
• Questions	23.6
Chapter 24 : Anti-anxiety Agents Drugs	24.1 - 24.4
24.1 Introduction	24.1
24.1.1 Molecular Mechanism Involved in Anxiety	24.1
24.2 Antianxiety Agents	24.2
24.2.1 Benzodiazepines	24.2
24.2.2 Buspirone	24.4
24.2.3 Hydroxyzine	24.4
• Questions	24.4
Chapter 25 : Anti-manics Drugs	25.1 - 25.4
25.1 Introduction	25.1
25.2 Antimanic Drugs	25.2
25.2.1 Lithium Carbonate	25.2
• Questions	25.4
Chapter 26 : Hallucinogens	26.1 - 26.4
26.1 Introduction	26.1
26.2 Effects of Hallucinogens	26.2
• Questions	26.4
Chapter 27 : Drugs used in Parkinson's Disease and Alzheimer's Disease	27.1 - 27.8
27.1 Parkinson's Disease	27.1
27.1.1 Symptoms of Parkinson's Disease	27.1
27.1.2 Causes of Parkinson's Disease	27.2
27.1.3 Molecular Mechanism of Parkinson's Disease	27.2
27.2 Antiparkinsonian Agents	27.3
27.2.1 Pharmacology of important Antiparkinsonian Agents	27.4
27.3 Alzheimer's Disease	27.6
27.3.1 Drug Therapy	27.8
27.3.2 Mechanism of Antialzheimer Agents	27.8
27.3.3 Pharmacology of Antialzheimer Agents	27.8
• Questions	27.8

Chapter 28 : CNS Stimulants and Nootropics

28.1 - 28.6

28.1 CNS Stimulants

28.1

28.1.1 Classification

28.1

28.1.2 Pharmacological Action

28.3

28.2 Nootropics

28.4

28.2.1 Nootropics that Improve Memory

28.5

• Questions

28.6

Chapter 29 : Opioid Analgesics and Antagonists

29.1 - 29.8

29.1 Introduction

29.1

29.2 Opioids

29.2

29.3 Opioid Receptors

29.2

29.3.1 Mechanism of Action of Opioid Drugs

29.3

29.3.2 Pharmacology of Opioid Drugs

29.4

29.4 Narcotic Antagonist

29.7

• Questions

29.8

Chapter 30 : Drug Addiction, Drug Abuse, Tolerance and Dependence

30.1 - 30.3

30.1 Drug Addiction

30.1

30.1.1 Signs of Drug Addiction

30.2

30.1.2 Treatment

30.2

30.2 Drug Abuse

30.2

30.3 Drug Tolerance

30.2

30.4 Drug Dependence

30.3

• Questions

30.3

• References

R.1 - R.1

Chapter ... 1

INTRODUCTION TO PHARMACOLOGY

♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- ❖ To know historical landmarks and scope of pharmacology.
 - ❖ To know advantages and disadvantages of different routes of drug administration.
 - ❖ Describe silent features of agonists, antagonists and spare receptors.
-

1.1 INTRODUCTION

The word pharmacology is derived from two Greek words, *pharmacon* meaning a drug, and *logos* meaning study. It can be defined as:

- "The science which deals with the history, source, physical properties, chemical properties, compounding, biochemical effects, physiological effects, mechanism of action, absorption, distribution, biotransformation, excretion, therapeutic and other uses of drugs, is called Pharmacology."
- "The study of a substance that interacts with the living system through chemical processes especially by binding to regulatory molecules and activates or inhibits normal body processes".
- "The science of substances used to prevent, diagnose and treat disease."

Pharmacology is the science of drugs. It is the study of chemical substances that interact with the living things by chemical processes, especially by binding to regulatory molecules, i.e. receptors. In 1847, Rudolph established the first institute of pharmacology.

Drug: The word drug comes from a French word '*Droque*' meaning a dry herb. It can be defined as: "Substance or material that is used or intended to be used to modify or explore physiological processes or pathological states, for the benefit of the recipient."

1.2 HISTORICAL LANDMARKS IN PHARMACOLOGY

1. Primitive men gathered the knowledge of healing and medicine by observing the nature, noticing animals while ill and by personal experiences after consuming certain herbs and berries as remedies **Hippocrates** (460B.C.-377B.C.) "The Father of Medicine" was the first to attempt to separate the practice of medicine from religion and superstition, developed his pledge of proper conduct for doctors.
2. Ebers Papyrus describes more than 700 drugs in extensive pharmacopoeia of that civilization. Included in this are: beer, turpentine, berries, poppy, lead, salt and crushed precious stones etc.
3. **Dhanvantari**: An early Indian medical practitioner and one of the world's first surgeons, regarded as the source of Ayurveda. He perfected many herbal based cures and natural remedies and was credited with the discovery of the antiseptic properties of turmeric and the preservative properties of salt which he incorporated in his cures.
4. **Susruta**: Ancient Hindu Medical Text Describes 760 herbs, Charka Samhita describes more than 650 drugs of animal, plant and mineral origins are used.
5. **Paracelsus (1493-1541)**: Pioneered the use of chemicals and minerals (zinc) in medicine. Vigorously opposed polypharmacy, or the prescription of multiple ingredients in a single medicine.
6. Willow bark was used to treat fever and pains. Extract of foxglove plant, used to treat dropsy (congestive heart failure) in 1785, contains digitoxin and digoxin; today called digitalis. William Withering (1741-1799) discovered digitalis. Synthetic organic chemistry was born in 1828, when Friedrich Wohler synthesized urea from inorganic substances and thus demolished the vital force theory.
7. **François Magendie**: A French physiologist, considered as pioneer of experimental physiology. He is known for describing the foramen of Magendie. There is also the cerebellum studied the action of *Nux vomica* (a strychnine-containing plant drug) on dogs, and showed that the spinal cord was the site of its convulsant action. His work was presented to the Paris Academy in 1809 (1783-1855). François Magendie established the idea of experimental physiology (an idea further popularized by Claude Bernard), he described in detail the effects of strychnine injections on animal subjects and also proved that the poison reached the animal's spinal cord by the blood stream and not (as was then commonly believed) by the lymphatic system. Because of such experiments, Magendie was able to introduce into French medicine a variety of new drugs, including morphine, codeine, quinine and strychnine.
8. **Claude Bernard**: A French Physiologist further expanded work of Francois Megendie. In 1842, Claude Bernard discovered that the arrow poison curare acts at the

neuromuscular junction to interrupt the stimulation of muscle by nerve impulses. Also k/a Father of Modern Experimental Medicine Bernard's experiments changed medicine (1813-1878). Claude Bernard's Contributions. The discovery of the role of the pancreatic secretion in the digestion of fats (1848). The discovery of a new function of the liver - the "internal secretion" of glucose into the blood (1848). The production of sugar by washed excised liver (1855) and the isolation of glycogen (1857). The demonstration that curare specifically blocks motor nerve endings (1856). He also established the existence of Vasomotor system and observed Vasodilatation and Vasoconstriction.

9. **R. Buchheim (1820-1879):** Buchheim built the world's 1st pharmacology laboratory at his own expense in the basement of his home. Buchheim is remembered for his pioneer work in experimental pharmacology. He introduced the bioassay to pharmacology.
10. **Oswald Schmiedeberg (1838-1921):** Generally recognized as the founder of modern pharmacology. Schmiedeberg obtained his medical doctorate in 1866 with a thesis on the measurement of chloroform in blood. In 1872, he became professor of pharmacology at the University of Strassburg. In 1878, he published a classic text, Outline of Pharmacology. In 1885, he introduced urethane as hypnotic.
11. **Otto Loewi:** A German Pharmacologist, brilliantly obtained his doctor's degree with a thesis about "techniques of isolations of frog's heart. He designed his most famous experiment, which provided the first evidence for the existence of chemical transmission in a synapse. The legend tells that he had the idea of the experiment in a dream and that he ran to the lab in the middle of the night. The experiment was very simple and became a prototype for all investigations of chemical factors in the nervous system. He cut out two hearts from frogs and perfused them with a warm physiological solution (Ringer). He then stimulated the vagus nerve to one of the hearts. As a consequence, there was a strong inhibition in this heart beats (R). The second heart was unaffected. However, when he perfused the second heart with the outflow of the perfusion of the first one, he achieved exactly the same effect (D). It was therefore concluded that some substance produced at the parasympathetic synapse level in heart R, was able to induce a similar response in the muscles of heart D (acetylcholine).
12. **Sir Henry Hallet Dale:** An English Pharmacologist Received his M.D. from Cambridge in 1909. Worked under John Langle and Paul Ehrlich, also a Fast friend of Otto Loewi. He distinguished Muscarinic and Nicotinic receptors in 1914. First identified acetylcholine in 1914 as a possible neurotransmitter, Loewi showed its importance in the nervous system. He introduced Dale's principle (Dale's Law) and Dale's Vasomotor Reversal Phenomenon.

- 13. Colonel Ram Nath Chopra:** He is known as Father of Indian Pharmacology. He first introduced and done systematic study of Rauwolfia serpentine. He had a major contribution in establishing the 1st National Drug Research Institute of India, Lucknow (presently known as Central Drug Research Institute, CDRI). He pioneered research on herbal drugs in India.
- 14. Paul Ehrlich (1854-1915):** German scientist in the fields of hematology, immunology, and chemotherapy. He is noted for curing syphilis and for his research in autoimmunity. He coined the term chemotherapy and popularized the concept of a magic bullet. Also coined the term Receptor (earlier called as receptive substance by Langley). Ehrlich skillfully transformed diphtheria antitoxin along with Emil Adolf von Behring, into an effective preparation, which is his first world renowned achievement. Also known as Father of Chemotherapy.
- 15. Alexander Fleming (1881-1955):** Scottish biologist and pharmacologist. His best-known discoveries are the discovery of the enzyme lysozyme in 1923, antibiotic penicillin from the mold *Penicillium notatum* in 1928 which was a discovery by chance.
- 16. Gerhard Domagk (1895-1964):** A German pathologist and bacteriologist done extensive work on infections and antibiotics credited with the discovery of Sulfonamidochrysoidine, the first commercially available antibiotic (marketed under the brand name Prontosil). He found the sulfonamide Prontosil to be effective against streptococcus, and treated his own daughter with it, saving her from the amputation of an arm. In 1939, Domagk received the Nobel Prize in Physiology or Medicine for this discovery, the first drug effective against bacterial infections.

1.3 SCOPE OF PHARMACOLOGY

The field encompasses various scopes throughout such as the following:

- Drug composition.
- Synthesis and drug design.
- Molecular and cellular mechanism.
- Organ/system mechanism.
- Signal transduction/cellular communication.
- Interaction.
- Toxicology.
- Therapy.
- Medical applications.
- Pre-clinical/clinical studies.

1.4 BRANCHES AND DIVISIONS OF PHARMACOLOGY

Main branches and divisions of pharmacology include:

- Pharmacokinetics.
- Pharmacodynamics.
- Therapeutics.
- Chemotherapy.
- Toxicology.
- Clinical Pharmacology.
- Pharmacy.
- Pharmacognosy.
- Pharmacogenetics.
- Pharmacogenomics.
- Pharmacoepidemiology.
- Comparative Pharmacology.
- Animal Pharmacology.
- Pharmacoeconomics.
- Posology.

1. **Pharmacokinetics:** The word Pharmacokinetics is derived from two words, Pharmacon meanings drug and kinetics meaning putting in motion. It can be defined as: "The branch of pharmacology that deals with the absorption, distribution, metabolism and excretion of drugs and their relationship with the onset, duration and intensity of the drug effect." What the body does to the drug is pharmacokinetics.

For example, the absorption, distribution, metabolism and excretion of Paracetamol are included in Pharmacokinetics.

2. **Pharmacodynamics:** Pharmacodynamics is the branch of Pharmacology that deals with the mechanism of action of drug and the relation between the drug concentration and its effect. It is the study of physical and chemical effects of drugs on body, parasites and microorganisms. What the drug does to the body is pharmacodynamics.

For example, adrenaline acts on adrenal receptors, stimulates adeny cyclase system producing effects such as cardiac stimulation and hyperglycemia is studied in Pharmacodynamics.

3. **Therapeutics:** The branch of pharmacology that deals with the art and science of treatment of disease. It is the application of pharmacological information together with the knowledge of disease, for the prevention and cure of the disease.

4. **Chemotherapy:** Chemotherapy refers to the treatment of diseases by chemicals that kill the cells, especially those of microorganisms and neoplastic cells. It is classified into two divisions:

- (a) **Antibiotics:** A chemical substance produced from microorganism. On high dilution are capable of destroying or inhibiting the growth of other microorganisms. Examples include Erythromycin given for gram positive organisms and Aminoglycosides for gram negative organisms.
- (b) **Antineoplastics:** The agents or drugs treat cancer called antineoplastics. Examples include: **Methotrexate**, which is anticancer drug. It inhibits the dihydrofolate reductase and interferes with the DNA synthesis and repair. **Vinca alkaloids**, which bind tubulin of microtubules and arrest mitosis in metaphase.
5. **Toxicology:** Toxicology is the branch of pharmacology which includes the study of adverse effects of drugs on the body. It deals with the symptoms, mechanisms, treatment and detection of poisoning caused by different chemical substances. Study of poisonous substances are also called toxicology.
6. **Clinical Pharmacology:** Clinical pharmacology is the scientific study of drugs in man. It includes pharmacokinetic and pharmacodynamic investigations in healthy or diseased individuals. It also includes the comparison with placebos, drugs in the market and surveillance programmes. The main objectives of clinical pharmacology are:
- Maximize the effect of drug.
 - Minimize the adverse effects.
 - Promote safety of prescription.
7. **Pharmacy:** Pharmacy is the branch of Pharmacology and is the art and science of compounding by dispensing drugs, preparing suitable dosage form for administration to man and animals. The health profession blends health science with chemical science and effective use of drugs.
8. **Pharmacognosy:** Pharmacognosy is the identification of drugs by just seeing or smelling them. It is a crude method no longer used. Basically, it deals with the drugs in crude or unprepared form and study of properties of drugs from natural sources or identification of new drugs obtained from natural sources.
9. **Pharmacoeconomics:** Pharmacoeconomics deals with the cost of drugs. In this discipline the cost of one drug is compared with another for same use. The cheap drugs are preferred.
10. **Pharmacogenetics:** Branch of pharmacology dealing with the genetic variations that cause difference in drug response among individuals or population. Example includes succinyl choline which is a skeletal muscle relaxant used in general anaesthesia. It is metabolized by pseudocholine esterase and has short duration of action. The presence of enzyme is determined by the gene and lack of this is recessively inherited. This may lead to respiratory paralysis, apnea and death.
11. **Pharmacogenomics:** Pharmacogenomics is the broader application of genomic technologies to new drug discovery and further characterization of older drugs.

Recombinant DNA technology involves the artificial joining of DNA of one species to another. *E. coli* is mostly used. In this way we can get huge amounts of drug in purified form which is less antigenic. Examples include GH, interferon and vaccines.

12. Pharmacoepidemiology: Pharmacoepidemiology deals with the effects of drugs on a large population. The effects may be good or harmful. It is conducted in three ways:

(a) Cohort studies: Patients receiving drugs are collected and followed up to determine the outcomes. It is prospective (forward looking) research, however, is time consuming and lengthy.

(b) Case control studies: These are retrospective studies. They reverse the direction of scientific logic from forward looking to backward looking.

(c) Phase Trials: These include different phases:

- Human pharmacology (20 to 50 subjects), pharmacokinetics and pharmacodynamics of the drug are observed.
- Therapeutic exploration (50 to 300 subjects), drugs are compared with placebo. *→ treatment done before any therapeutic usage*
- Therapeutic confirmation (250 to 1000 subjects), safety, efficacy of drugs is compared with the drugs already present.
- Therapeutic use (2000 to 10000 subjects), the opinion of physicians prescribing the drugs is collected regarding dosage and efficacy. Surveillance programmes are lengthy when conducted outside hospitals.

13. Comparative Pharmacology: Branch of pharmacology dealing with the comparison of one drug to another belonging to the same or another group.

14. Posology: Posology deals with the dosage of drugs. Example includes paracetamol given as one tablet of 500 mg thrice a day.

15. Animal Pharmacology: Animal pharmacology deals with the different properties of drugs in animals. A vast variety of animals are utilized including rabbits, mice guinea pigs, etc. Drugs are given to the animals and all parameters (their behaviour, activities, vital signs, etc.) are recorded. Any change is noted down. If found to be useful in animals, then the drug is tested on humans.

1.5 SOURCES OF DRUGS

The six main sources of drugs include:

1. Plant sources.
2. Animal sources.
3. Mineral/ Earth sources.
4. Microbiological sources.
5. Semi-synthetic sources/Synthetic sources.
6. Recombinant DNA technology.

1. Plant Sources:

Plant source is the oldest source of drugs. Most of the drugs in ancient times were derived from plants. Almost all parts of the plants are used i.e. leaves, stem, bark, fruits and roots.

2. Animal Sources:

- Pancreas is a source of Insulin, used in treatment of Diabetes.
- Urine of pregnant women gives human chorionic gonadotropin (hCG) used for the treatment of infertility.
- Sheep thyroid is a source of thyroxin which is used in hypertension.
- Cod liver is used as a source of vitamins A and D.
- Anterior pituitary is a source of pituitary gonadotropins, used in treatment of infertility.
- Blood of animals is used in preparation of vaccines.
- Stomach tissue contains pepsin and trypsin, which are digestive juices used in treatment of peptic diseases in the past. Nowadays better drugs have replaced them.

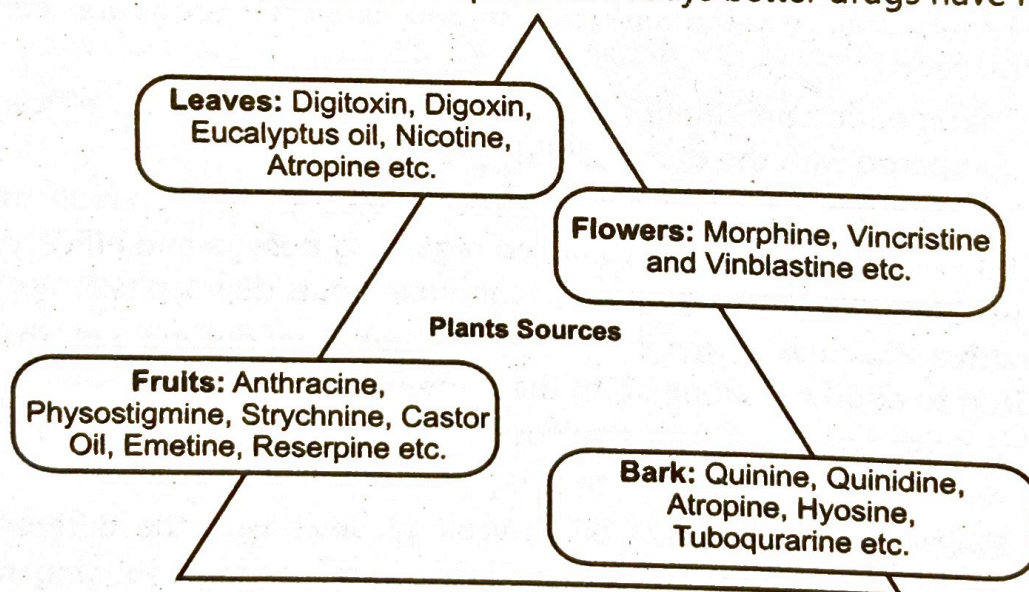


Fig. 1.1: Different sources of drug from Plants

3. Mineral Sources:

1. Iron is used in treatment of iron deficiency anemia.
2. Mercurial salts are used in Syphilis.
3. Zinc is used as zinc supplement. Zinc oxide paste is used in wounds and in eczema.
4. Iodine is antiseptic. Iodine supplements are also used.
5. Gold salts are used in the treatment of rheumatoid arthritis.
6. Fluorine has antiseptic properties.
7. Borax has antiseptic properties as well.
8. Selenium as selenium sulphide is used in anti-dandruff shampoos.
9. Petroleum is used in preparation of liquid paraffin.

4. Synthetic/Semi-synthetic Sources:

1. Synthetic Sources: Emetine Bismuth Iodide
2. Semi-synthetic Sources: Apomorphine, Diacetyl morphine, Ethinyl Estradiol, Homatropine, Ampicillin and Methyl testosterone.

5. Microbiological Sources:

1. *Penicillium notatum* is a fungus which produces penicillin.
2. Actinobacteria produces Streptomycin.
3. Aminoglycosides such as gentamicin and tobramycin are obtained from streptomycis and micromonosporas.

6. Recombinant DNA technology:

Recombinant DNA technology involves cleavage of DNA by enzyme restriction endonucleases. The desired gene is coupled to rapidly replicating DNA (viral, bacterial or plasmid). The new genetic combination is inserted into the bacterial cultures which allow production of vast amount of genetic material.

Advantages:

1. Huge amounts of drugs can be produced.
2. Drug can be obtained in pure form.
3. It is less antigenic.

Disadvantages:

1. Well-equipped lab is required.
2. Highly trained staff is required.
3. It is a complex and complicated technique.

1.6 ROUTES OF DRUG ADMINISTRATION

Routes of administration greatly affect bioavailability by changing the number of biologic barriers, a drug must cross or by changing the exposure of drug to pumping and metabolic mechanisms. Different routes used for drug administration include:

1. Enteral route
2. Parenteral route
3. Inhalation route
4. Topical route

1. Enteral Route:

Enteral administration involves absorption of the drug via the GI tract or alimentary canal and includes oral, gastric or duodenal (e.g., feeding tube), and rectal administration. Enteral route is through the alimentary canal. It might be:

- Oral
- Sublingual
- Per rectum

(a) Oral Route: Oral (PO) administration is the most frequently used route of administration because of its simplicity and convenience, which improve patient compliance. It is mostly used for the neutral drugs. It may be in the form of tablets, capsules, syrup, emulsions or powders.

Advantages:

1. It is convenient.
2. It is the cheapest available route.
3. It is easy to use.
4. It is safe and acceptable.

Disadvantages:

1. Less amount of drug reaches the target tissue.
2. Some of the drug is destroyed by gastric juices e.g. adrenaline, insulin, oxytocin
3. Absorption has to take place which is slow, so it is not preferred during emergency.
4. It might cause gastric irritation.
5. It might be objectionable in taste.
6. It might cause discoloration of teeth e.g. iron causes staining, tetracyclines below 14 years cause brown discoloration so not it is advisable during pregnancy.

First Pass Effect: First pass effect is the term used for hepatic metabolism of drug when absorbed and delivered through portal blood. Greater the first pass effect, less amount of the drug reach the systemic circulation.

(b) Sublingual Route: Sublingual route involves tablets placed under the tongue or between cheeks or Gingiva. Sublingual administration is advantageous for drugs that have low oral availability because venous drainage from the mouth bypasses the liver. Drugs must be lipophilic and are absorbed rapidly. Buccal formulations can provide extended-release options to provide long-lasting effects. The drugs given by this route include nitroglycerin, isoprenaline and oxytocin. Nifedipine used for the treatment of hypertension in emergency is given by sublingual route.

Advantages:

1. Rapid absorption takes place.
2. Drug is dissolved easily.
3. Drug enters the blood directly.
4. Less first pass effect.
5. Spitting out of the drug removes its effect.

Disadvantages:

1. This method is inconvenient.
2. Irritation of the mucous membrane might occur.
3. Person may swallow the drug.
4. Might be unpleasant in taste.

(c) Rectal Route: Rectal administration via suppositories to produce a systemic effect is useful in situations in which the patient is unable to take medication orally (e.g. unconscious, vomiting, convulsing). Drugs are absorbed through the rectal mucosa.

Advantages:

1. This route is preferred in unconscious or uncooperative patients.
2. This route avoids nausea or vomiting.
3. Drug cannot be destroyed by enzymes.
4. This route is preferred if drug is irritant.

Disadvantages:

1. This route is generally not acceptable by the patients.
2. Drugs given by rectal route have 50% first pass metabolism.

2. Parenteral Route:

Parenteral administration refers to any routes of administration that do not involve drug absorption via the GI tract (*par* = around, *enteral* = gastrointestinal), including the intravenous (IV), intramuscular (IM), subcutaneous (SC or SQ), and transdermal routes. Reasons for choosing a parenteral route over the oral route include drugs with low oral bioavailability, patients who are unable to take the drug by mouth (e.g., it irritates the GI tract), the need for immediate effect (e.g., emergency situations), or the desire to control the rate of absorption and duration of effect. Parenteral route includes:

- **Injections:** Intra muscular, Intravenous, Intraarterial, Intracardiac, Intrathecal, Intraosseous - into bone - marrow, Intrapleural, Intraperitoneal, Intraarticular, Intradermal (Intracutaneous), Subcutaneous route (Hypodermic).
- **Inhalation: Hypospray or jet injections.**

Advantages:

1. Parenteral route is rapid.
2. It is useful for uncooperative patients.
3. It is useful for unconscious patients.
4. Inactivation by GIT enzymes is avoided.
5. First pass effect is avoided.
6. Bioavailability is 100%.
7. Immediate action takes place.
8. This route is preferred in emergency situations and for unconscious patients.
9. Titration of dose is possible.
10. Large volume of fluids might be injected by this route.
11. Diluted irritant might be injected.
12. Absorption is not required.
13. Blood plasma or fluids might be injected.

Disadvantages:

1. Skill is required.
2. It is painful.
3. This method is expensive.

4. It is less safe.
5. There is no retreat.
6. This method is more risky.
7. Sepsis-Infection might occur.
8. Phlebitis (Inflammation of the blood vessel) might occur.
9. Infiltration of surrounding tissues might result.
10. This method is not suitable for oily and insoluble preparations.

3. Inhalation:

Drugs administered by inhalation through the mouth must be atomized into smaller droplets than those administered by the nasal route, so that the drugs can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs drugs pass depends on the size of the droplets. Smaller droplets go deeper, which increases the amount of drug absorbed. Inside the lungs, they are absorbed into the bloodstream. Examples include aerosols like salbutamol; steam inhalations include tincture and Benzoin.

Advantages:

1. Rapid absorption takes place.
2. Rapid onset of action takes place.
3. This route has minimum side effects.
4. No first pass effect takes place.
5. This method is easy.
6. Fewer doses is required.

Disadvantages:

1. Special apparatus is required.
2. Irritation of the respiratory tract may take place.
3. Cooperation of the patient is required.
4. Airway must be patent.

1. Topical route:

Drugs may be applied to the external surfaces, the skin and the mucous membranes. Topical route includes:

- (a) **Enepidermic route:** When the drug is applied to the outer skin, it is called enepidermic route of drug administration. Examples include poultices, plasters, creams and ointments.
- (b) **Epidermic route (Innunction):** When the drug is rubbed into the skin, it is known as epidermic route. Examples include different oils.
- (c) **Insufflations:** When drug in finely powdered form is blown into the body cavities or spaces with special nebulizer, the method is known as insufflations.
- (d) **Instillation:** Liquids may be poured into the body by a dropper into the conjunctival sac, ear, nose and wounds. Solids may also be administered.

- (e) **Irrigation or Douching:** This method is used for washing a cavity e.g. urinary bladder, uterus, vagina and urethra. It is also used for application of antiseptic drugs.
- (f) **Painting/Swabbing:** Drugs are simply applied in the form of lotion on cutaneous or mucosal surfaces of buccal, nasal cavity and other internal organs.

Time for drugs Action using Different Routes of Administration

Drugs take different time durations after injection using different routes to perform their actions. This time delay is important, oral route has controlled release time, thus depot or reservoir preparation may be made e.g. penicillin for rheumatic fever. Usage of drug depends on its physical properties, chemical properties, speed of action, need and bypass effect. Some of the approximate time intervals are given below:

Table 1.1: Time for Drug Action using different Routes of Administration	
Route of Drug Administration	Delay time for Action
Intravenous route	30-60 seconds
Intraosseous route	30-60 seconds
Endotracheal inhalation	2-3 minutes
Sublingual route	3-5 minutes
Intramuscular route	10-20 minutes
Rectal route	5-30 minutes
Ingestion	30-90 minutes

1.7 AGONISTS

An agonist is a drug that binds to a receptor and produces a functional response. Examples include morphine (μ -opioid receptor) and clonidine (α_2 -adrenoceptor). The ability to produce a response is termed efficacy (or intrinsic activity); this varies with the type of response measured. Agonist has been derived from Latin word agnista, which means contender. The agonist drug is one that brings about a reaction.

Direct-Binding Agonist: This agonist drug works the same as the neurotransmitters in the brain, and they bind themselves to the site of the receptor. The maximum effect of drug depends upon closely release of drug in brain tissue. Classic examples of these direct-binding agonist drugs include nicotine, found in cigarettes and vaping devices, dopamine, and apomorphine.

Indirect-Acting Agonist: This agonist drug enhances the actions that the neurotransmitters have on the brain, encouraging and stimulating release of them, basically upping the amount which are released. One example of an indirect-acting agonist drug is cocaine.

1.8 ANTAGONISTS

Neutral antagonists block the effect of an agonist. There are two types of antagonism: competitive (reversible, surmountable) and non-competitive (irreversible, insurmountable). For example, naloxone is a competitive antagonist at all opioid receptors and ketamine is a non-competitive antagonist at the NMDA-glutamate receptor. Antagonist has been derived from Latin antagonista and from Greek antagonistes, which means "competitor, rival or opponent." In short, antagonist drugs will block the neurotransmitters, and there are two types:

Direct-Acting Antagonist: The receptors in the brain that would usually be occupied by the neurotransmitters are blocked. The direct-acting antagonist drug basically takes up that space so the neurotransmitters can't. It means that the connection can't happen. One example of a direct-acting antagonist drug is Atropine.

Indirect-Acting Antagonist: This drug stops the release of the neurotransmitters entirely, once again blocking them from working. One example of an indirect-acting antagonist is Reserpine.

Receptor antagonists can be classified as reversible or irreversible. Reversible antagonists readily dissociate from their receptor; irreversible antagonists form a stable, permanent or nearly permanent chemical bond with their receptor (e.g. by alkylation). Pseudo-irreversible antagonists slowly dissociate from their receptor.

In **competitive antagonism**, binding of the antagonist to the receptor prevents binding of the agonist to the receptor.

In **non-competitive antagonism**, agonist and antagonist can be bound simultaneously, but antagonist binding reduces or prevents the action of the agonist.

In **reversible competitive antagonism**, agonist and antagonist form short-lasting bonds with the receptor, and a steady state among agonist, antagonist, and receptor is reached. Such antagonism can be overcome by increasing the concentration of the agonist. For example, naloxone (an opioid receptor antagonist that is structurally similar to morphine), when given shortly before or after morphine, blocks morphine's effects. However, competitive antagonism by naloxone can be overcome by giving more morphine.

1.9 SPARE RECEPTORS (RESERVE RECEPTORS)

Maximal efficacy means a state at which receptor mediated signaling is maximal and that; further increase in the drug dose does not produce any additional response. Theoretically, it should happen when all the receptors get occupied by the drug. But normally when drugs act on receptors to produce the response all the receptors are not occupied to produce the maximal response by a full agonist i.e. each cell or tissue has some receptors unoccupied which may be called spare receptors.)

Spare Receptor History: Furchgott (1964) showed in an experiment that adrenaline induced contraction of the rabbit aortic strips did not require complete occupation of the

α -adrenoceptors in the aortic strips for obtaining maximal response. Nickerson (1957) using histamine on a guinea pig ileum preparation. In both cases, only small percentage of receptors had to be occupied by agonist to produce maximum contraction. The rest of the receptor were 'Spare' or 'Reserve' receptor. The term spare receptors were proposed by Stephenson.

Concept of Spare Receptors:

1. Maximum response is elicited by agonist at a concentration that does not require full occupancy of the receptor.
2. They are not hidden or unavailable.
3. When they are occupied, they can be coupled to respond.
4. They are not differ from non-spare receptor.

Examples:

1. The amplitude of muscle twitches in response to Ach. Acetylcholine blocked by addition of toxin (curare). This toxin occupies at least 50% of receptors. But still maximum response can be demonstrated. That means, at least 50% of receptor were spare in sense that they were not required for completely normal twitch of Ach.
2. Myocardium also contains large population of spare receptor because the maximal inotropic response to catecholamine can be elicited even when only less than 10% of receptor occupied.
3. Maximal stimulation of steroidogenesis by Leydig cells occurs when only 1% of LH receptor is occupied. Full steroid induced transcriptional response may only require 10% receptor.
4. About 90% of insulin-receptors are just serving as spare receptors. Thus there is an immense functional reserve to make sure that adequate amount of glucose enters into cell.

Clinical Significance:

1. The spare receptor concept could explain why the sensitivity of tissue depends on both affinity of drug and total number of receptor.
2. It is possible to change the sensitivity of tissue with spare receptor by altering receptor concentration.
3. An important biological consequence of spare receptor is that it allows low affinity agonists to produce full response at low concentration. This is important because low affinity agonist dissociate rapidly from receptor leading to short biologic response. High affinity agent show slow dissociates rates and slower reversal or termination of response.
4. In analyzing pharmacological properties of ligands or interpreting results with receptor mutants in heterologous expression systems, which often have very high levels of receptor expression, it is essential to understand and account for the spare receptor phenomenon. Many compounds that are partial agonist in normal tissues, are full agonist in expression system due to high receptor number.

1.10 ADDICTION

Addiction is a complex condition in which a person engages in use of a substance or in a behavior for which the rewarding effects provide a compelling incentive to repeatedly pursue the behavior despite detrimental consequences. People with addiction (severe substance use disorder) have an intense focus on using a certain substance(s), such as alcohol or drugs like opioids, cocaine, nicotine, and others, to the point that it takes over their life. They keep using alcohol or a drug even when they know it will cause problems. According to the National Institute on Drug Abuse, people begin taking drugs for a variety of reasons, including:

1. To feel good — feeling of pleasure, "high".
2. To feel better — e.g., relieve stress.
3. To do better — improve performance.
4. Curiosity and peer pressure.

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

1.11 TOLERANCE

Tolerance is defined as a person's diminished response to a drug that is the result of repeated use. Tolerance can develop with both illicit drugs and prescription medications. It is a physical effect of repeated use of a drug, not necessarily a sign of addiction. For example, patients with chronic pain frequently develop tolerance to some effects of prescription pain medications without developing an addiction to them. A person with a drug tolerance has to take larger doses in order to achieve the same effect as they did earlier in their drug use.

Types of Tolerance:

1. **Acute Tolerance:** It is caused by repeated exposure to a drug over a relatively short period of time. Cocaine abuse often results in acute tolerance.
2. **Chronic Tolerance:** It develops when an individual's body adapts to constant exposure to a drug over weeks or months. People who regularly abuse prescription opioids build up chronic tolerance to the euphoric effects of these medications, leading many of them to increase the dosage taken or switch to more potent ways of taking these drugs, such as snorting or injecting.
3. **Learned Tolerance:** It result from frequent exposure to certain drugs. For example, people who abuse alcohol for months or years often do not appear intoxicated to others.
4. **Physiological Tolerance:** It describes the body's adaptation to repeated drug exposure.

5. **Metabolic or Pharmacokinetic Tolerance:** It could result from an increase in the rate of drug metabolism after repeated drug exposures. For example, the induction of metabolic enzymes for the drug could produce metabolic tolerance.
6. **Functional or Pharmacodynamic Tolerance:** It results from a decrease in the way CNS receptors respond to the drug after repeated drug exposures. A down-regulation of receptors (i.e., fewer) or a reduction in receptor affinity or efficacy could produce a functional tolerance effect. Finally, cross-tolerance may occur, where the development of tolerance to one drug conveys tolerance to drugs within the same class or acting on similar CNS mechanisms.

1.12 DEPENDENCE

Drug dependence applies to any drug, including alcohol that is consumed repeatedly in spite of the negative consequences the drug use is having on the life of the drug user and the lives of those around the user. Drug dependence indicates the drug user is dependent on the drug either physically, psychologically or both in order to function in everyday life. The words dependence and addiction are often used interchangeably, but there are important differences between the two. In medical terms, dependence specifically refers to a physical condition in which the body has adapted to the presence of a drug. If an individual with drug dependence stops taking that drug suddenly, that person will experience predictable and measurable symptoms, known as a withdrawal syndrome.

Dependence is caused by changes in the body as a result of constant exposure to a drug. In the case of prednisone, the body adapts to repeated doses of the drug by decreasing its own cortisol production, which can leave the body without a baseline level of cortisol "support" when prednisone use is stopped resulting in steroid withdrawal symptoms until the normal balance is re-established.

1.13 TACHYPHYLAXIS

Tachyphylaxis means diminished response to later increments in a sequence of applications of a physiologically active substance, such as the diminished pressor response that follows repeated injections of renin. The pharmacological term tachyphylaxis is used to describe rapidly occurring response desensitization, a situation where the biological response to a given drug dose diminishes when it is given continuously. This pharmacological phenomenon is well observed in some drug categories such as ephedrine, nitrates, beta blockers and H_2 antagonists. The major homeostatic mechanisms responsible for tachyphylaxis in many cellular systems involve either a change in the number of receptors, or a change in the ability of a receptor to affect the downstream signaling molecules. Tachyphylaxis differs from drug tolerance in that it is an acute rather than a gradual consequence of prolonged drug administration.

1.14 IDIOSYNCRASY

In pharmacology, idiosyncrasy refers to an idiosyncratic reaction, which is an adverse effect to an agent, such as a drug, which does not occur in most patients who have used the same agent. Drug idiosyncrasy or idiosyncratic response, are infrequent and believed to result from a genetically determined metabolic or enzyme deficiency that is not expressed

under normal situations. These responses show a dose-response relationship, but not the same one shown by the average patient. Example of idiosyncrasy: Hemolytic anemia occurring in patients with glucose-6-phosphate dehydrogenase deficiency after receiving an oxidant drug. Another example, an antipsychotic drugs such as chlorpromazine and clozapine cause infrequent reactions such as rhabdomyolysis (breakdown of striated muscle) and liver toxicity.

1.15 ALLERGY

Allergy is a condition involves an exaggerated reaction by the immune system in response to exposure to certain foreign substances. The response is exaggerated because these foreign substances are normally seen by the body as harmless in non-allergic individuals and do not cause a response in them. In allergic individuals, the body recognizes the foreign substance, and the allergic part of the immune system generates a response. Allergy-producing substances are called "allergens." Examples of allergens include pollens, dust mites, molds, animal proteins, foods, and medications. When an allergic individual comes in contact with an allergen, the immune system mounts a response through the IgE antibody. People who are prone to allergies are said to be allergic or "atopic."

Most Common Types:

- **Drug allergy:** An abnormal reaction of the immune system to a medication.
- **Food allergies:** An unpleasant or dangerous immune system reaction after a certain food is eaten.
- **Contact dermatitis:** A skin rash caused by contact with a certain substance.
- **Latex allergy:** An allergic reaction to certain proteins found in natural rubber latex.
- **Allergic asthma:** Asthma triggered by exposure to the same substances that trigger allergy symptoms.
- **Seasonal allergies:** An allergic response causing itchy, watery eyes, sneezing and other similar symptoms.
- **Animal allergy:** An abnormal immune reaction to proteins in an animal's skin cells, saliva or urine.
- **Anaphylaxis:** A severe, potentially life-threatening allergic reaction.
- **Allergy to mold:** An abnormal allergic reaction to mould spores.

QUESTIONS

1. Define the term pharmacology.
2. Define the terms Pharmacokinetics and Pharmacodynamics.
3. Enlist the sources of drugs with examples.
4. Write advantages and disadvantages of oral route of drug administration.
5. Write advantages and disadvantages of parenteral route of drug administration.
6. Write advantages and disadvantages of topical route of drug administration.
7. Explain the various route of drug administration.
8. Define the terms Idiosyncrasy and Allergy.

Chapter ... 2

PHARMACOKINETICS

◆ LEARNING OBJECTIVES ◆

After completing this unit, reader should be able to:

- ❖ Describe the various mechanisms of drug absorption.
- ❖ To know various factors affecting drug absorption, distribution, biotransformation and elimination.
- ❖ Describe the biochemical reactions involved in biotransformation of drug.

2.1 INTRODUCTION

Pharmacokinetics (PK), derived from the Greek words *pharmacon* (drug) and *kinetikos* (movement), is used to describe the absorption, distribution, metabolism, and excretion of a compound. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient. The goal of pharmacokinetics is an enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

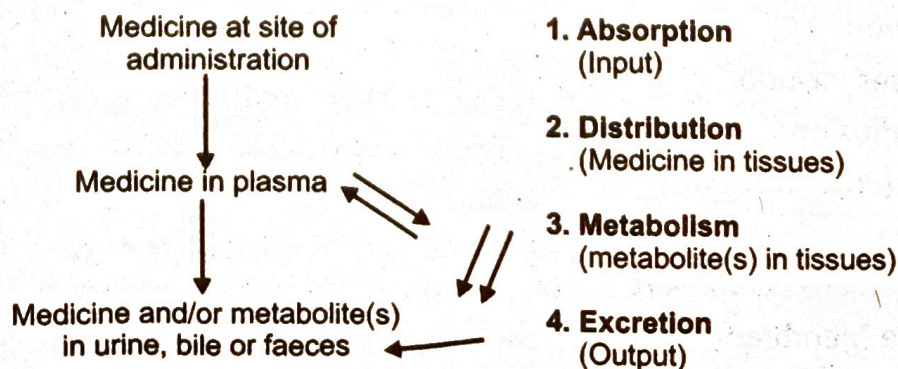


Fig. 2.1: Schematic representation of the absorption, distribution, metabolism and excretion of medicines

(2.1)

2.2 BIOLOGICAL MEMBRANE

Biological membranes consist of a double sheet (known as a bilayer) of lipid molecules. This structure is generally referred to as the phospholipid bilayer. Biological membranes consist of a lipid bilayer separating different compartments, with protein molecules acting as enzymes, channels or carrier proteins. Drugs have to cross the biological membranes to get absorbed.

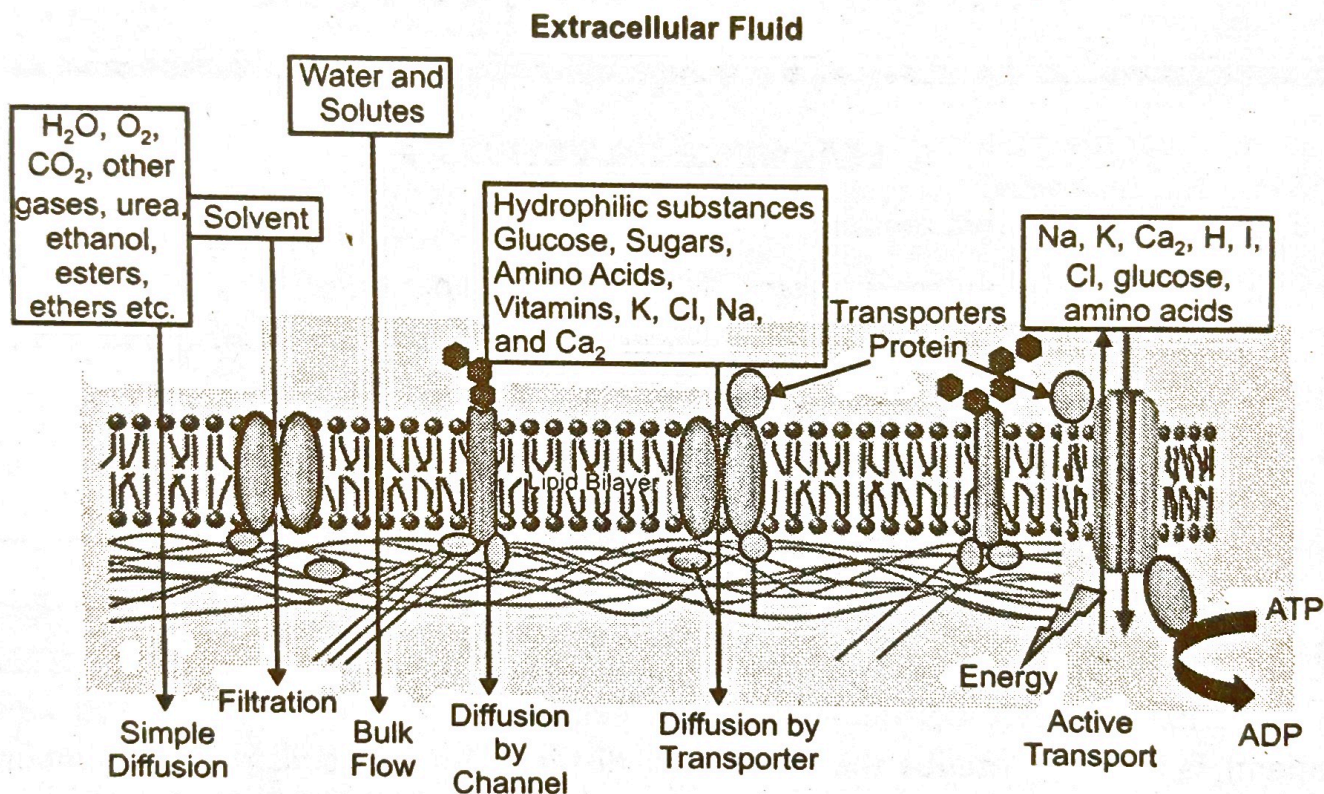


Fig. 2.2: The plasma membrane or lipid bilayer membrane

2.3 MECHANISM OF DRUG ABSORPTION

Absorption is the process by which drug molecules cross biological membranes. It is usually associated with oral drugs and their absorption through the GIT. It also occurs by subcutaneous, intra muscular and transdermal routes of administration of drugs. However, the absorptive process does not occur during direct injection of drug by intravenous or intraarterial injection.

These processes include:

1. Simple Diffusion
2. Filtration (Pore transport)
3. Bulk Flow
4. Carrier Mediated Transport
 - (a) Active Membrane Transport
 - (b) Facilitated Transport
5. Endocytosis
 - (a) Phagocytosis
 - (b) Pinocytosis

2.3.1 Simple Diffusion

Most of the drugs are absorbed by simple diffusion, which is the movement of molecules down the concentration gradient i.e. from higher concentration to lower concentration. This type of transport occurs mostly for the lipid soluble drugs. This type of transport is non-specific i.e. no carrier proteins are required. No energy is required for this type of transport.

Factors affecting diffusion:

Concentration Gradient across Membrane: Fick's law of diffusion explains the concentration gradient across the membrane. It is stated as the flux of molecules per unit time is equal to the concentration gradient times, the area times, the permeability coefficient divided by the thickness.

$$\text{Flux (molecules/unit time)} = (C_1 - C_2) \times \text{Area} \times \frac{\text{Permeability coefficient}}{\text{Thickness}}$$

Where permeability coefficient is the motion of drug molecules across the membrane.

Thus, Fick's law indicates that the movement of molecules is directly proportional to the concentration gradient, area and the permeability coefficient and is inversely proportional to the thickness of the membrane.

- 1. Molecular/ Particle Size:** Molecular size is the size of a single molecule. The particle size is different for different preparations of the same drug. More the particle size, slow is the diffusion and absorption. Therefore, if we want to have slower time of absorption, we can make the particle size larger.
- 2. Membrane Surface Area:** More is the surface area of the membrane, more is the absorption. Stomach and intestinal lining are the main areas of absorption for the oral drugs. Thus, the absorption is greater in the small intestine due to the large surface area.
- 3. Lipid Water Particle Coefficient:** Membranes have a thin water layer on them. Therefore, part of the drug must dissolve in the water film, while most of the remaining portion is lipid soluble. If the lipid water particle coefficient is large, more diffusion will occur due to greater lipid solubility. In cases of small lipid water particle coefficient, less diffusion will occur due to the less lipid solubility.
- 4. Ionization of Drugs:** Most of the drugs are either weak acids or weak bases. Therefore, they are partly ionized and partly unionized. The ionized portion is charged, which attracts water molecules, thus forming large complexes. These complexes cannot cross the membranes because they are fewer lipids soluble. This is why the ionized part of the drugs cannot cross the membrane. Drugs are better absorbed in unionized form. Decreasing pH by one unit, 91% of acid would become unionized and 91% of base would become ionized. Decreasing pH by two units, 99% of acid would become unionized.

Acidic drugs: Acidic drugs on dissociation give anion and proton.



Basic drugs: Basic drugs on combining with a proton become an anion.



The existence of drugs as neutral or charged particles depends on the pH.

Acidic Medium: In acidic medium, lots of protons are present. Therefore, greater amount of acidic drug is unionized (shift towards left of equation 2.1). Thus in acidic medium acidic drug is present more in unionized form, which increases its absorption. This is why acidic drugs are better absorbed from the stomach.

Basic drugs get ionized in acidic medium (right shift of equation 2.2), thus this form is poorly absorbed. Aspirin, an acidic drug is unionized in acidic medium of stomach, so is easily absorbed.

Basic Medium: The opposite is true in case of basic medium. Acidic drugs are poorly absorbed while the basic drugs are well absorbed. Quinidine and pyrimethamine are antimalarial and basic, so are ionized in stomach and unionized in intestines, from where they are absorbed.

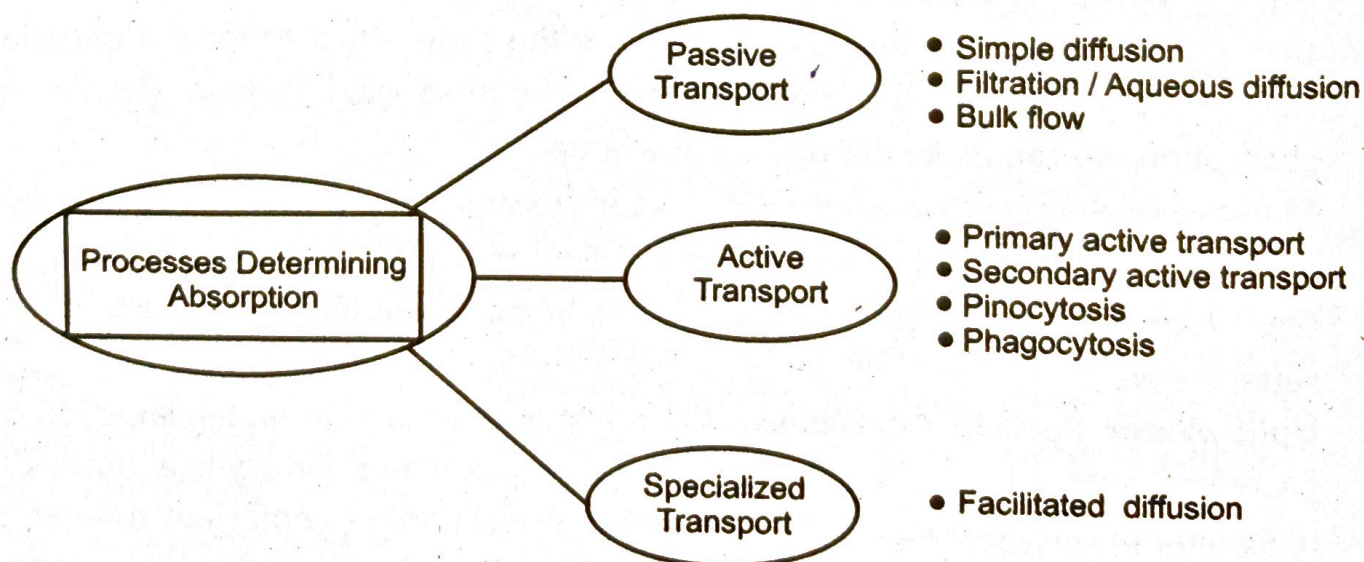


Fig. 2.3: Process determining drug absorption

- 1. Protonated/Unprotonated form:** Protonated form of acidic drugs is well absorbed while the protonated form of basic drugs is poorly absorbed, due to the reasons given above.
- 2. Ionization Coefficient:** Ionization coefficient is the pH at which the drug is 50% ionized and 50% unionized. For acidic drugs, pKa is lower, while that for basic drugs is higher.

Henderson Hasselbalch Equation: This can be stated as:

$$pK_a - pH = \log [P/UP]$$

Where, P is the protonated form while UP is the unprotonated form.

If pH is lower than pKa the value will be positive indicating that the protonated form is more than the unprotonated form.

For acidic drugs: If pH is lower than pKa, AH will be more.

$$pK_a - pH = \log \left[\frac{AH}{A^-} \right]$$

For basic drugs: If pH is lower than pKa, BH⁺ will be more.

$$pK_a - pH = \log \left[\frac{BH^+}{B} \right]$$

Drugs in Intestines: For acidic drugs A⁻ is more, so the drugs are present in ionized form in the intestines, thus drugs are less absorbed. But as the surface area of the stomach is small while that of intestines is very large, even acidic drugs are more absorbed from the upper part of the intestine.

For basic drugs, B is more, thus is present in unionized form in the intestines and is absorbed in a much greater quantity. In short we can say that acidic drugs are better absorbed in the acidic medium while basic drugs are better absorbed in the basic medium.

Ion trapping: Most of the drugs are reabsorbed from the proximal tubules of kidneys. Acidic drugs are better reabsorbed from acidic urine. This is an important fact, which can be manipulated to get desired results, as is the case of poisoning with acidic drugs. If we make the urine alkaline (by administering sodium bicarbonate), decreased reabsorption of acidic drugs take place, a phenomenon known as **ion trapping**.

In case of poisoning with basic drug, urine can be made more acidic (by administering ammonium chloride), by virtue of which the basic drug becomes ionized and is not reabsorbed, with the result that more of it is excreted out.

2.3.2 Filtration

Filtration involves the aqueous channels or pores through which hydrophilic drugs can pass. Filtration occurs in the jejunum and proximal tubules of kidneys. It is absent in the stomach and the lining of the urinary bladder. Only certain ions like Na⁺ and drugs of low molecular weight, like ethanol and glycerol can undergo filtration.

2.3.3 Bulk Flow

The drug in this process passes through the pores between capillary endothelial cells. The passage is independent of water and lipid solubility. Bulk flow is the phenomenon mostly seen with the intra muscular and subcutaneous injections. Drug is injected in bulk form into the muscle. Drug molecules along with the aqueous medium pass through the pores of endothelium, and diffuse into the blood. This type of transport is independent of pH and pKa. Bulk flow does not occur in brain because of absence of pores. However, bulk flow is dependent on the blood flow, more the blood flow, more rapid is the absorption. This is why the area is rubbed after intra muscular injections to increase the blood flow.

2.4 CARRIER MEDIATED TRANSPORT

2.4.1 Active Membrane Transport

Active membrane transport is for the drugs which cannot cross the lipid membrane and require transport proteins. Their structure is similar to the endogenous substances undergoing active transport like amino acids, sugars, neurotransmitters, which have the transport proteins. Active transport is the carrier mediated transport.

The drug moves against the concentration gradient. Energy in the form of ATP is required for the process to occur. Different drugs bind different proteins, thus their absorption is selective from different areas, as well as their distribution. Some drugs directly affect the brain like the Levo Dopa, which utilize amino acid transporting mechanism. Other examples include methyl dopa for hypertension and fluorouracil which is anticancer drug. Active transport mechanism is saturable and can be inhibited by competing drugs.

Primary Active Transport: When the substance moves against the concentration gradient by the expenditure of energy, the process is called primary active transport.

Secondary Active Transport: When the substance moves against the concentration gradient by the energy stored by a substance moving down the concentration gradient, the process is called secondary active transport.

2.4.2 Facilitated Transport

Facilitated transport involves the drug moving down the concentration gradient by the help of transport proteins. No energy expenditure is required. This type of transport is also specific and saturable. The main objective is that lipid insoluble drugs become lipid soluble by combining with the carrier. E.g. iron binds with apoferritin and certain catecholamines enter the nerve cells by this process.

2.4.3 Endocytosis

(a) Phagocytosis

Phagocytosis is also known as *cell eating*. This type of transport is utilized by large molecular weight drugs.

e.g. uptake of vitamin B₁₂ along with intrinsic factor.

e.g. anticancer drugs.

(b) Pinocytosis:

Pinocytosis or cell drinking requires expenditure of energy. Fat soluble vitamins, protein molecules and folic acid enter the cells by this process.

Table 2.1: Difference between various transport mechanisms

Simple Diffusion	Facilitated Diffusion	Active Transport
Down concentration gradient	Down concentration gradient	Against concentration gradient
No energy required	No energy required	Energy required
No carrier protein involved	Carrier proteins involved	Carrier proteins involved
Non-specific	Specific	Specific
Non-saturable	Saturable	Saturable
Lipid soluble drugs	Non-diffusible drugs	Lipid insoluble drugs

2.5 FACTORS AFFECTING ABSORPTION OF DRUGS

The various factors which can affect the absorption of drugs, mainly categorised into Pharmaceutical factors and patient related factors, details given in Fig. 2.4.

Factors Related to Drugs or Pharmaceutical Factors:

1. **Lipid water solubility:** Lipid water solubility coefficient is the ratio of dissolution of drug in lipid as compared to water. Greater the lipid water solubility coefficient more is the lipid solubility of the drug and greater is the absorption. Less the coefficient, less is the lipid solubility and less is the absorption. Water film exists on the membranes so part of the drugs must be water soluble to cross this water film. Drugs with benzene ring, hydrocarbon chain, steroid nucleus and halogen groups in their structures are lipid soluble.
2. **Molecular size:** Smaller the molecular size of the drug, rapid is the absorption. There exist different processes involved in absorption for different molecular sizes. Those with a large molecular size undergo endocytosis or facilitated diffusion, while those with smaller molecular sizes utilize aqueous diffusion or lipid channels.
3. **Particle size:** Particle may be composed either of a single molecule or more than hundred molecules. Larger is the particle size, slower will be the diffusion and absorption and vice versa.
4. **Degree of Ionization:** Different drugs are either acidic or basic and are present in ionized or unionized form, which is given by their pKa values. In the body, the ratio of the ionized and unionized forms depend on the pH of the medium. Acidic drugs are unionized in the acidic medium and basic drugs are unionized in the basic medium. Acidic drugs are better absorbed from the acidic compartment.
5. **Physical Forms:** Drugs may exist as solids, liquids or gases. Gases are rapidly absorbed than the liquids, while the liquids are rapidly absorbed than the solids. Thus the drugs in syrup or suspension form are rapidly absorbed than the tablets or capsules. Volatile gases used in general anesthesia are quickly absorbed through the pulmonary route.
6. **Chemical Nature:** Chemical nature is responsible for the selection of the route of administration of drug. Drugs that cannot be absorbed through the intestines are given by the parenteral route. Example include heparin which is large molecular weight, and cannot be given orally. Similarly, benzyl penicillin is degraded in the GIT, so is given parenterally. Salt forms of drugs are better absorbed than the organic compounds when given orally. The organic compounds are given by routes

other than the oral or enteral route. Drugs in inorganic form are better absorbed than organic forms e.g. iron in Fe^{+2} is better absorbed than Fe^{+3} , d-tubocurarine exists in ionized form and is a quaternary ammonium compound. Neostigmine is also a quaternary ammonium compound.

7. **Dosage Forms:** Dosage forms affect the rate and extent of absorption. A drug can be given in the form of tablets, capsules or transdermal packets. Injections may be aqueous or oily. This changes the rate of absorption. Example include nitroglycerin which when given by sublingual route, disintegrates rapidly but stays for a shorter duration. When it is given orally, it disintegrates slowly and stays for longer duration. When given by transdermal route, the drug can cover an even longer duration.

- (a) **Disintegration:** Disintegration is the breaking up of the dosage form into smaller particles. When drug disintegrate rapidly, absorption will be rapid.
- (b) **Dissolution:** After disintegration, the drug dissolves in the gastric juices, which is called dissolution. It is only then that the drug can be absorbed. When these two processes occur rapidly, the rate of absorption increases.

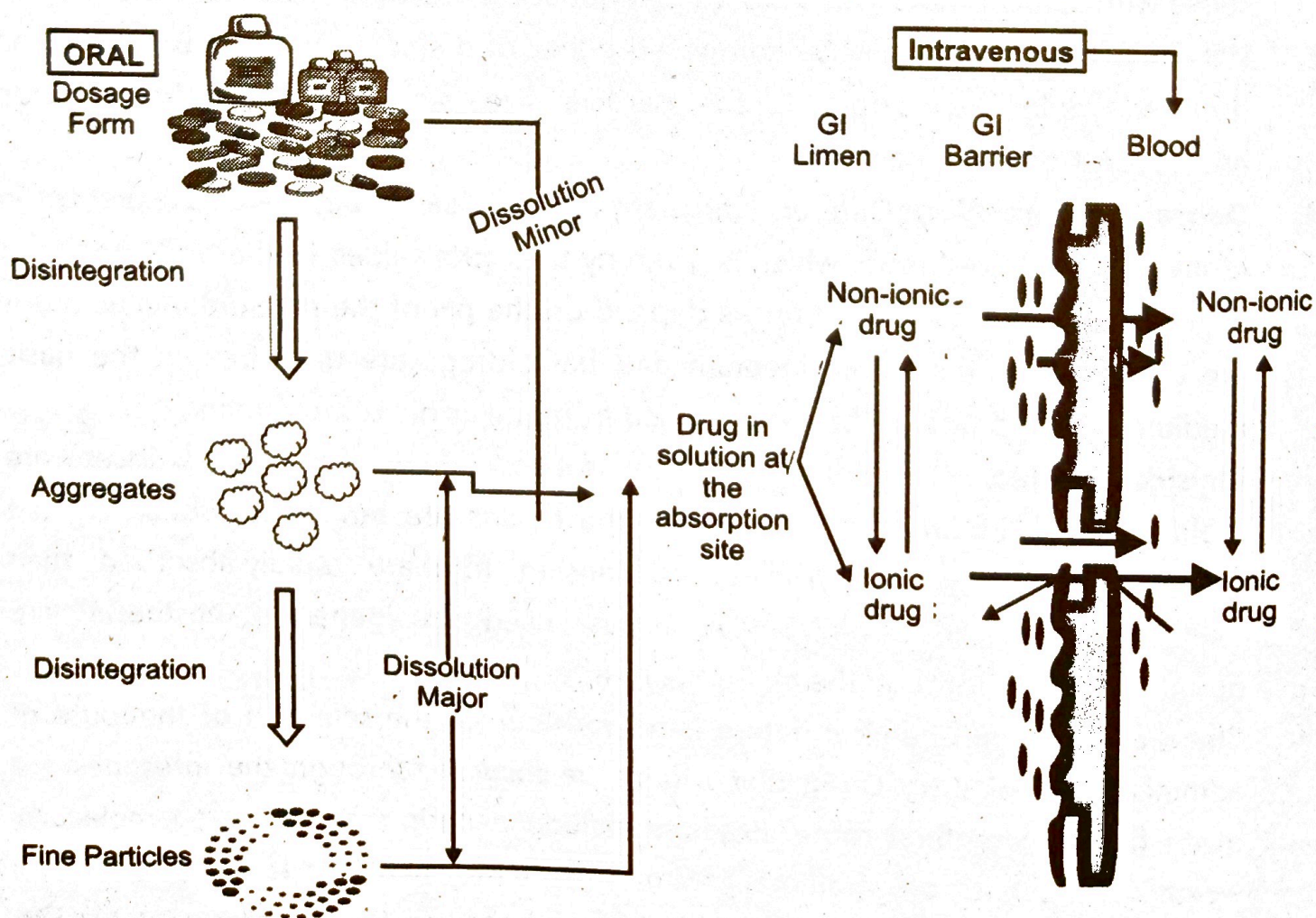


Fig. 2.4: Sequence of events in the absorption of drugs

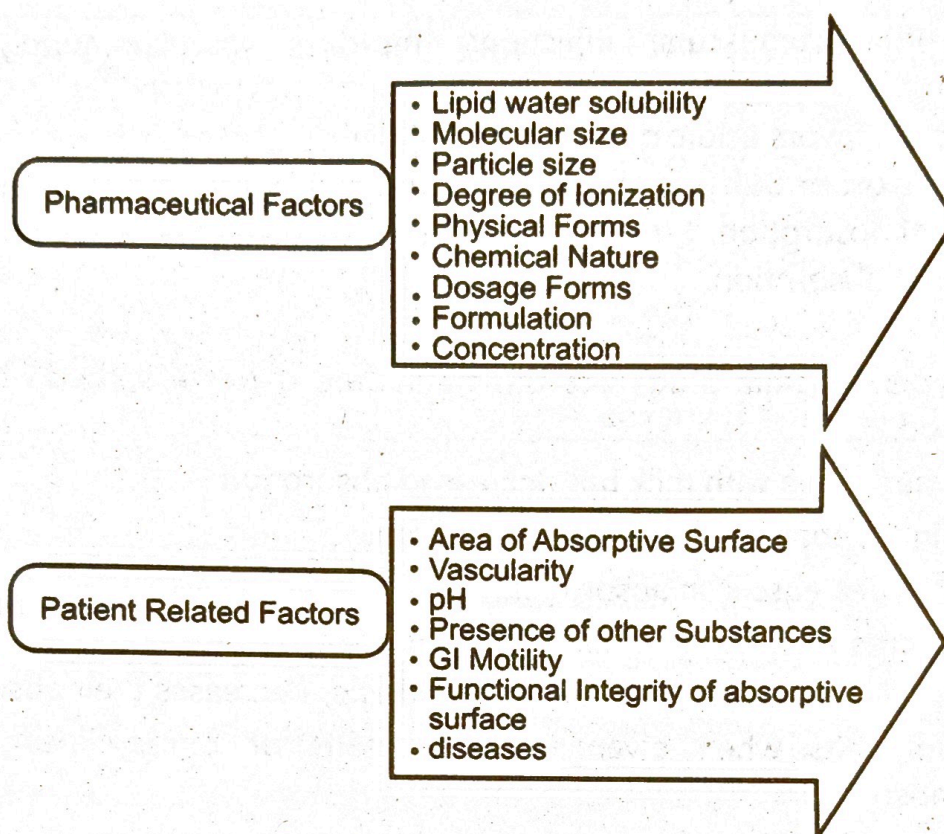


Fig. 2.5: Pharmaceutical factors and patient related factors affects the absorption of drugs

8. **Formulation:** When the drugs are formed, apart from the active form some inert substances are included. These are the diluents, excipients and the binders. Normally they are inert, but if they interact, they can change the bioavailability. Example include Na^+ which can interact to decrease the absorption. Atropine is required by some patients only in amounts of 0.2 to 0.6 mg.
9. **Concentration:** According to Fick's law, higher the concentration more flux occurs across the membrane. The rate is less affected than the extent of absorption.

Factors Related to Body or Patient Related Factors:

1. **Area of Absorptive Surface:** Area of absorptive surface affects oral as well as other routes. Most of the drugs are given orally because of the large area of absorptive surface, so that greater absorption occurs. Intestinal resection decreases the surface area leading to a decreased absorption. Similarly, when the topically acting drugs are applied on a large surface area, they are better absorbed. Organophosphate compounds are highly lipid soluble and poisoning can occur even by absorption through skin.
2. **Vascularity:** More the vascularity more is the rate and extent of absorption and vice-versa. In shock, blood supply to the GIT is less so the oral route of drug administration is affected. The blood flow to the peripheries is decreased, so absorption in those areas is diminished as well. Therefore, intravenous route is preferred in case of shock. Vasoconstrictors decrease the blood supply of an area, thus are useful to restrict the local anesthetics so that they remain for a longer duration. They are wash away as well as their toxic effects are decreased in this way.

Massage in intramuscular injections improves vascular supply to enhance absorption.

3. **pH:** Acidic pH favors acidic drug absorption while basic pH is better for basic drugs.
4. **Presence of other Substances:** Foods or drugs may interact with the drugs to alter their rate of absorption. Especially for the drugs given orally, food can increase or decrease the absorption.

Examples:

- Antihyperlipidemic drugs like the statins are better absorbed when taken with the food.
 - Iron when given with milk has decreased absorption.
 - Vitamin C enhances the absorption of iron.
 - Phytates decrease iron absorption.
 - Milk decreases the absorption of tetracyclines.
 - Epinephrine when given with local anesthetics decreases their absorption.
 - Calcium salts when given with iron salts or tetracyclines interfere with their absorption
 - Aspirin is given with food while antibiotics are given in empty stomach. Liquid paraffin may affect drug absorption. Some acidic drugs bind with cholestyramine to form a complex which is not absorbed in GIT.
5. **GI Mobility:** GI mobility must be optimal for absorption of oral drugs. It should be neither increased nor decreased which may affect the rate or extent of absorption. Different diseases or drugs may alter the mobility. Diarrhoea causes rapid peristalsis, decreasing contact time and thus the extent of absorption is affected more. Constipation affects disintegration and dissolution so decreases motility.
 6. **Functional Integrity of Absorptive Surface:** Flattening and edema of mucosa decrease absorption. Dysfunctional breach in the skin affects the absorption of topical drugs. Parasympathomimetic drugs can decrease drug absorption and parasympatholytic drugs can increase absorption. Metopramide prevents vomiting and accelerates gastric emptying. It increases gastric emptying increasing drug absorption.

Table 2.2: Influence of Drug pKa on Site of absorption of drug

Drugs	pKa	pH/site of absorption
Very weak acids e.g. pentobarbital Hexobarbital	>8	Unionized at all pH values; Absorbed along the entire length of GIT
Moderately weak acids e.g. aspirin Ibuprofen	2.5 – 7.5	Unionized in gastric pH and ionized in intestinal pH; better absorption from stomach
Stronger acids e.g. disodium cromoglylate	< 2.0	Ionized at all pH values; Poorly absorbed from GIT

Drugs	pKa	pH/site of absorption
Very weak bases e.g. theophylline Caffeine	< 5.0	Unionized at all pH values; Absorbed along entire GIT
Moderately weak bases e.g. codeine	5 – 11	Ionized at gastric pH, unionized at intestinal pH; better absorption from intestine.
Stronger bases e.g. guanethidine	> 11	Ionized at all pH values; Poorly absorbed from GIT

7. Diseases:

- **Diarrhoea:** Decreases absorption because of decreased contact time.
- **Malabsorptive syndrome:** Decreases absorption.
- **Achlorhydria:** Acidic medium for acidic drugs is affected.
- **Cirrhosis:** Cirrhosis affects portal circulation. Thus, affecting metabolism of drugs.
- **Emphysema:** Emphysema affects the absorption of volatile gases through the pulmonary route.
- **Lipodystrophy:** Lipodystrophy decreases absorption. In diabetics, insulin might lose its affect.

2.6 DISTRIBUTION OF DRUGS

Drug enters the body by absorption. Inside the body, drugs move in the blood to different parts of the body. Distribution of drugs can be defined as: "The process by which a drug reversibly leaves the blood stream and enters the interstitium (extracellular fluid) and/or the cells or tissues." The average circulation time of blood is 1 minute. Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the antibiotic rifampin, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs. The drugs are present in free or bound form and different processes or mechanisms affect their distribution. Distribution is defined as it is the reversible process in which drug transfer from one compartment to another.

Compartments for Distribution:

1. Plasma
2. Interstitial fluid
3. Intracellular fluid
4. Transcellular fluid

Physiological Barriers for Drug Distribution:

1. Simple Endothelial Capillary Wall Barrier
2. Simple Cell Membrane Barrier.
3. Blood Brain Barrier.
4. Blood Cerebrospinal Fluid Barrier.
5. Placental Barrier.
6. Blood Testis Barrier.

1. Capillary Endothelial Barrier: All drugs (ionized, non-ionized) with molecular size less than 600 daltons diffuse through the capillary endothelium.

2. Cell Membrane Barrier: Once a drug diffuses from the capillary wall into extracellular fluid, its further entry into cells of most tissues is limited by its permeability through membrane (Similar to lipoidal barrier).

3. Blood-Brain Barrier: The capillary membrane between the plasma and brain cells is much less permeable to water-soluble drugs than is the membrane between plasma and other tissues. Thus, the transfer of drugs into the brain is regulated by the blood-brain barrier. To gain access to the brain from the capillary circulation, drugs must pass through cells rather than between them. Only drugs that have a high lipid-water partition coefficient can penetrate the tightly apposed capillary endothelial cells.

The tight junctions in BBB are made by cerebral endothelial cells at their boundaries where they assemble (limit the aqueous paracellular pathways connecting the outer and inner environment). There is discontinuous distribution of pericytes along the cerebral capillaries and partly enclose the endothelium. A network is formed by foot processes from astrocytes which surround the capillaries completely. Axons from neurons also adjoin closely against the endothelial cells and hold vasoactive neurotransmitters and peptides. Microglia (perivascular macrophages) are the occupant immune-competent cells of the brain and are resultant of systemic circulating monocytes and macrophages

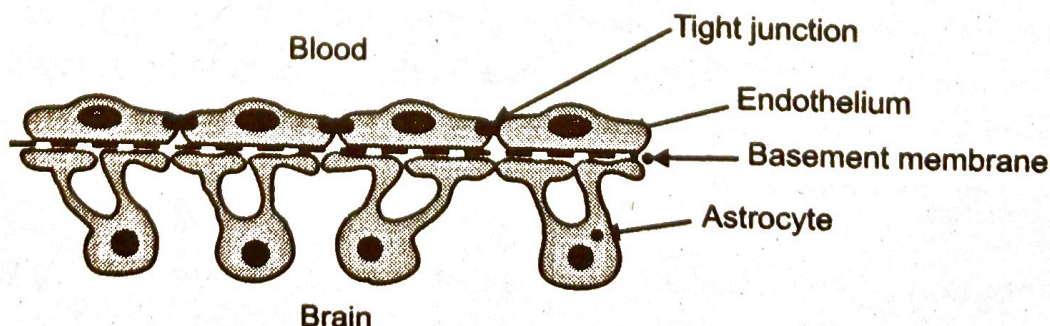


Fig. 2.6: Blood-brain barrier

The term blood-brain barrier denotes the barrier separating the brain tissue from the blood circulation. The structural basis consists of three parts:

- (a) Layer of endothelial cells interconnected through tight junctions and not containing fenestrations (normally present in endothelium of other tissues).
- (b) Basal membrane consisting of basal lamina of astrocytes and basal lamina of endothelial cells.

(c) Protrusions of astrocytes, so called pedicles, which anneal on the basal membrane.

Inflammation, such as occurs in bacterial meningitis or encephalitis, may increase the permeability of the blood-brain barrier, permitting the passage of ionized lipid-insoluble compounds (e.g., penicillin and ampicillin) that would otherwise be restricted from penetrating into the brain extracellular fluid.

4. Blood-CSF Barrier: Cerebrospinal fluid (CSF) formed by choroid plexus of lateral, third and fourth ventricles. Choroid cells are joined together by tight junction forming blood-CSF barrier.

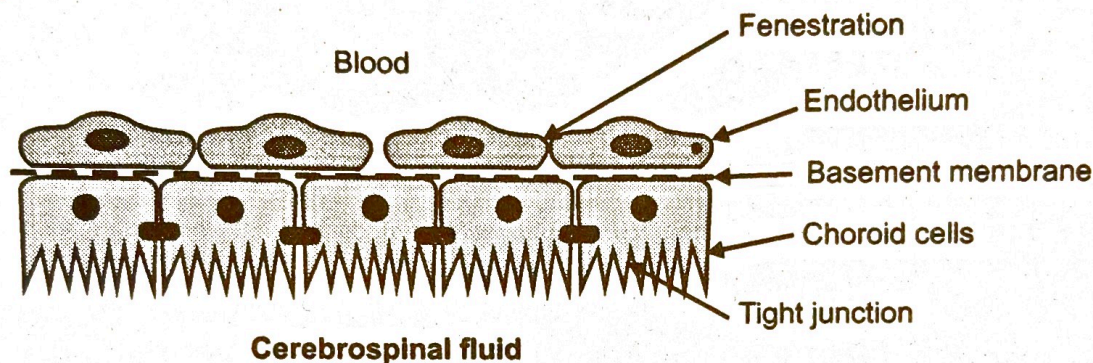


Fig. 2.7: Blood-CSF Barrier

Blood-CSF barrier separates the cerebrospinal fluid and blood. Similar to hematoencephalic barrier, it consists of three structurally distinct parts:

1. Choroidal epithelial cells interconnected by tight junctions (which are more permeable than the junctions between the endothelial cells of brain capillaries) and secreting the cerebrospinal fluid. The side facing the liquor has its surface enlarged by the presence of projections called microvilli.
2. Basal membrane.
3. Endothelium of the pia mater capillaries containing fenestrations.

5. Placental Barrier: The blood vessels of the fetus and mother are separated by a number of tissue layers that collectively constitute the placental barrier. Drugs that traverse this barrier will reach the fetal circulation. The placental barrier, like the blood-brain barrier, does not prevent transport of all drugs but is selective, and factors that regulate passage of drugs through any membrane (e.g. pKa, lipid solubility, protein binding) are applicable here. In general, substances lipid soluble cross the placenta with relative ease in accordance with their lipid-water partition coefficient and degree of ionization. Highly polar or ionized drugs do not cross the placenta readily. However, most drugs used in labor and delivery are not highly ionized and will cross. They are generally weak bases with pKa values of about 8 and tend to be more ionized in the fetal bloodstream, since the pH of fetal blood is around 7.3 as compared with the maternal blood pH of 7.44. Differences in maternal and fetal blood pH can give rise to unequal concentrations of ionizable drugs in the mother and the fetus.

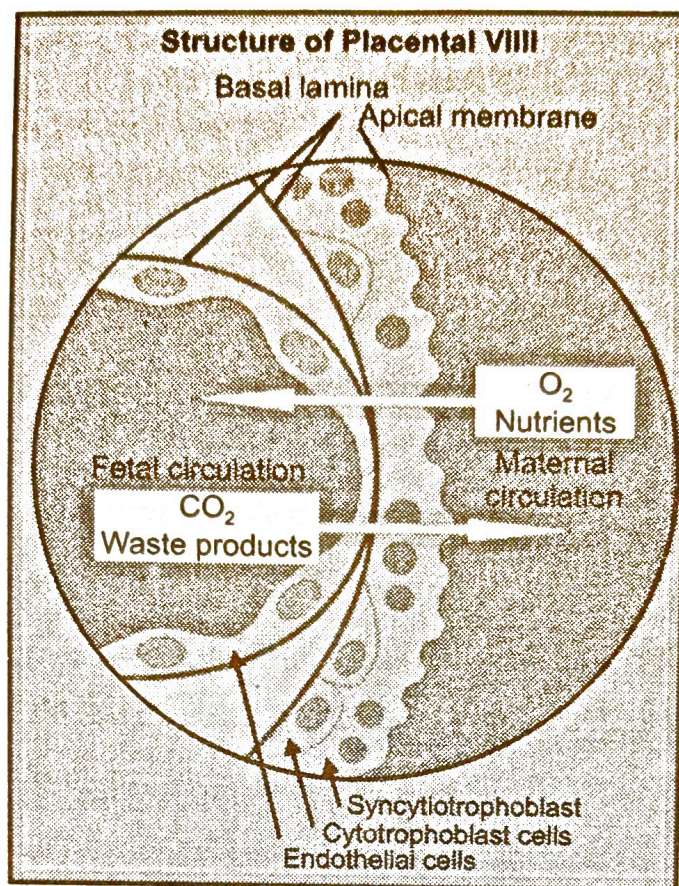


Fig. 2.8: Placental Barrier

6. Blood-Testis Barrier: The existence of a barrier between the blood and testes is indicated by the absence of staining in testicular tissue after the intravascular injection of dyes. Morphological studies indicate that the barrier lies beyond the capillary endothelial cells and is most likely to be found at the specialized Sertoli-Sertoli cell junction.

2.6.1 Factors Affecting Distribution

Factors affecting distribution of drugs include those related to the drug and those related to the body.

Pharmaceutical factors:

- 1. Lipid Solubility:** Greater the lipid solubility, more is the distribution and vice-versa.
- 2. Molecular size:** Almost all drugs having molecular weight less than 500 to 600 Daltons easily cross the capillary membrane to diffuse into the extracellular fluid (ECF). Only small, water-soluble molecules and ions of size below 50 Daltons enter the cell through water channels. Larger molecules are transported through specialised transport system existing on the cell membrane. Larger the size, lesser the distribution. Smaller sized drugs are more extensively distributed.
- 3. Degree of Ionization:** Blood and ECF pH normally remains constant at 7.4; they do not have much of an influence on drug diffusion unless altered in conditions such as systemic acidosis or alkalosis. Most drugs are either weak acids or weak bases and their degree of ionization at plasma or ECF pH (i.e. 7.4) depends upon their pKa. All the drugs that ionize plasma pH (i.e. polar hydrophilic drugs) cannot penetrate the lipoidal cell membrane and tissue permeability is the rate determining step. Only the unionized drugs which are generally lipophilic rapidly cross the cell membrane. Species which has greater K_o/w (partition coefficient) penetrates well.

Examples:

- Pentobarbital and Salicylic acid have same K_o/w but pentobarbital is more unionized at blood pH than salicylic acid and hence distributes rapidly.
- Thiopental, a nonpolar, lipophilic drug, largely unionized at plasma pH readily diffuses into the brain.
- Penicillins are polar, and ionized at plasma pH, hence does not cross the blood-brain-barrier.

4. **Cellular binding:** Drugs may exist in free or bound form. Bound form of drugs exists as reservoirs. The free and bound forms co-exist in equilibrium. Cellular binding depends on the plasma binding proteins.

Tissue binding: Different drugs have different affinity for different cells. All cells do not bind the same drugs.

5. **Duration of Action:** The duration of action of drugs is prolonged by the presence of bound form while the free form is released. This leads to a longer half-life and duration of action of drug.
6. **Therapeutic Effects:** Bisphosphonate compounds bind with the bone matrix cells and strengthen them. They are used in the treatment of osteoporosis.
7. **Toxic Effects:** Chloroquine can be deposited in the retina. Tetracycline can bind the bone material. It may also get bound to the enamel of the teeth.

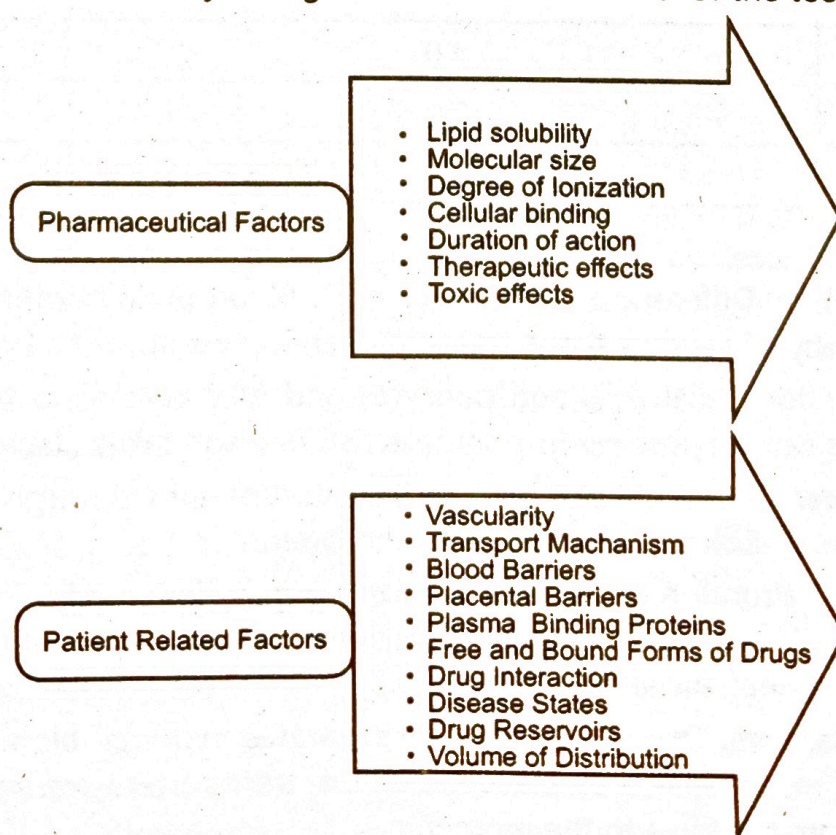


Fig. 2.9: Pharmaceutical factors and patient related factors affects the distribution of drugs

Patient Related Factors:

1. **Vascularity:** Most of the blood passes through the highly profused organs (75%) while the remaining (25%) passes through the less profused areas. Therefore, most

of the drugs go first to the highly perfused areas. They may get bound to these organs. They are then redistributed to the less perfused areas like the skin and the skeletal muscles. This phenomenon is common among the lipid soluble drugs.

Example includes thiopentone sodium which is used as general anesthetic. When given, it goes to the brain producing its effects. It is then redistributed to the less perfused organs. Because of high lipid solubility, it is accumulated in the fatty tissue for longer duration. Thus the clearance of the drug is slow, producing prolonged period of drowsiness (up to 24 hours).

2. **Transport Mechanism:** Different drugs are taken up by different compartments of the body differently. Lipid soluble drug move by passive transport which is non-specific. Active transport occurs only where carrier proteins are present.

Table 2.3: Blood Perfusion Rate

Organ	Perfusion Rate (ml/min/ml of tissue)	% of cardiac output
Bone	0.02	5
Brain	0.5	14
Fat	0.03	4
Heart	0.6	4
Kidneys	4.0	22
Liver	0.8	27
Muscle	0.025	15
Skin	0.024	6

3. **Blood Barriers:** Different blood barriers exist. Blood brain barrier is present because of the delicacy of nervous tissue to avoid chemical insult to the brain.

Structure: Endothelial cells and pericytes and glial cells form the barrier through which drugs cannot pass easily, only selective passage takes place.

Transporters: Certain efflux pumps or transporters exist through which drug can be effluxed as well. Example includes p-glycoprotein.

Disruption: Disruption of barrier may occur, e.g. by inflamed meningitis. Drugs may pass which might be toxic as well as beneficial i.e. during meningitis penicillin can pass which has beneficial effects.

4. **Placental Barriers:** Trophoblastic tissue separates maternal blood from fetal blood. Different transporters are present. Efflux transporters cause efflux back of the drugs from the fetus to the mother.
5. **Plasma Binding Proteins:** Drugs bound to plasma proteins cannot be distributed into tissue or eliminated and are inactive. Competition for binding could lead to increased side effects or toxicity. Many proteins exist in the plasma. Plasma binding proteins include:

- (a) **Albumin:** Albumin is the most abundant plasma protein. It has higher affinity for acidic drugs but the capacity is low. Only two sites are present for binding drug molecules. However, albumin can bind a large number of basic drugs but has lower attractive forces. Its capacity for binding basic drugs is more but the affinity is less.
- (b) **Globulins:** Globulins can bind hormones, vitamins, etc.
- (c) **Glycoproteins:** Alpha glycoproteins mainly bind basic drugs. Their levels are increased during stress, trauma and surgery. During these times that their more amounts are required.
- (d) **Lipoproteins:** Lipoproteins also bind some drugs.

6. **Free and Bound Forms of Drugs:** When drug enters the body, it exists in:

- Free form
- Bound form

These two forms have certain effects on the pharmacokinetics and pharmacodynamics. Free forms are metabolized and excreted because they can cross the glomerular membrane. Free forms of drugs are therapeutically active.

Bound forms of drugs act as a reservoir. They are not metabolized or excreted and do not have therapeutic or toxic effect. When the free form is used up, drug is released from the reservoirs. Thus, both forms exist in equilibrium.

Significance:

- Bound form acts as a reservoir, providing free form when required.
- Drugs having higher plasma protein binding if given in normal doses are only used in binding plasma proteins, with the result that less free form is available for therapeutic effect. Thus drugs having higher plasma protein binding are given in larger doses at the start. This is known as **loading dose**. This is ensure that enough free form of the drug is available. Higher plasma protein binding drugs include warfarin and phenytoin while those having negligible plasma protein binding include lithium, metronidazole and myxothiazol.

7. **Drug Interactions:** If a number of drugs are simultaneously given, or drugs interact with endogenous substances, one drug can be displaced by another.

Example includes interaction of sulphonamide with bilirubin, with the result that bilirubin is displaced which may cause kernicterus in babies. Drug interactions occur if both drugs bind to same protein and depends on:

- **Affinity:** Higher the affinity of the drug, more easily can it displace the other drug.
- **Concentration:** Higher concentration drug can displace the lower concentration drugs.

This phenomenon might be of consequence in the following situations:

- **Volume of Distribution:** The volume into which the drug is distributed is known as the volume of distribution. Drug can be distributed to different body compartments, it is diluted when goes to the different compartment. If

the drug has a small volume of distribution, it stays in the same compartment producing toxic effects. (Explained separately). Toxic effects are produced when more drugs are present in free form than usual.

- **Therapeutic Index:** Therapeutic index is the safety margin, the range in which the drug is safe. If drug has a large therapeutic index, then large concentrations of the drug are safe. If it has a small therapeutic index, it may move out of the safe range and cause toxic effects. Thus, the drug displacement phenomenon is significant in low therapeutic index drugs.

8. **Disease States:** Different diseases affect the distribution of drugs. Renal diseases cause hypoalbuminemia. Due to fewer proteins, toxic levels of free drugs may be present. Uremic by-products are also produced which compete with drugs. Hepatic diseases cause decreased synthesis of proteins causing hypoalbuminemia. Free drugs may be present in toxic levels and bilirubin by products increase as well. Thus drug, whose doses have to be adjusted to produce desired effects (may be reduced even to half).

9. **Drug Reservoirs or Tissue binding of drugs:** Drugs are stored and are released slowly which affects their pharmacokinetics and pharmacodynamics. Drug can bind to various tissues. Tissue-drug binding is important from two points of views:

- It increases the volume of distribution (by reducing the concentration of free drug in the plasma) and
- Drug bound to tissue acts as a reservoir and hence biological half-life increases.

For majority of drugs that bind to extravascular tissues, the order of binding is: Liver > Kidney > Lung > Muscle.

- **Liver:** Oxidation products of carbon tetrachloride and paracetamol bind irreversibly with liver tissues resulting in hepatotoxicity.
- **Kidneys:** Metallothionin, a protein present in the kidneys, binds to heavy metals such as lead, mercury and cadmium.
- **Lungs:** Basic drugs like imipramine, chlorpromazine and antihistamines accumulate in the lungs.
- **Skin:** Chloroquine and Phenothiazines accumulate in the skin by interacting with melanin pigment.
- **Hairs:** Arsenicals are deposited in hair shafts.
- **Bones:** Tetracycline binds to bones and teeth. Administration of tetracycline to infants or children during ontogenesis results in permanent brown-yellow colouration of teeth.
- **Adipose tissues:** Lipophilic drugs such as thiopental and pesticide like DDT accumulate in adipose tissues (fat tissues).
- **Nucleic acid:** DNA interacts with drugs like Chloroquine and quinacrine resulting in distortion its double helical structure.

10. Volume of Distribution: Volume of distribution (V_d) is the ratio between the amount of drug in body (dose given) and the concentration of the drug (C) measured in blood or plasma.

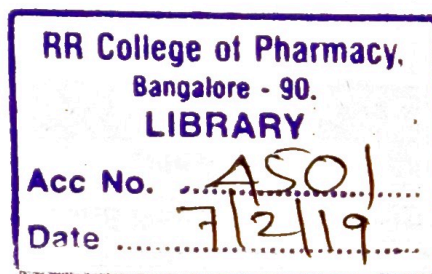
$$V_d = \frac{\text{(Amount of drug in body)}}{C}$$

where C is the concentration of drug in blood or plasma.

- V_d as calculated is an apparent volume of distribution. For example:
- V_d for digoxin is 440 L/70 kg (liters per 70 kg person)
- V_d for chloroquine is 13,000 L/70 kg (liters per 70 kg person)
- Such very large V_d would be consistent with very high tissue binding, leaving little free in plasma or blood
- V_d is an apparent volume of distribution, since V_d is the volume needed to contain the amount of drug homogeneously at the concentration found in the blood, plasma, or plasma water.
- Many drugs have a much higher concentration in extravascular compartments; therefore these drugs are not homogeneously distributed.

Physical volumes (L/kg body weight) for some body compartments:

- Water
 - Total Body Water (0.5-0.7 L/kg) or about 35000 to 49000 ml (70 kg individual)
 - Extracellular Water (0.2 L/kg)
 - Blood (0.08 L/kg);
 - Plasma (0.04 L/kg)
- Fat
 - 0.2 - 0.35 L/kg
- Bone
 - 0.07 L/kg



2.6.2 Factors Influencing the Volume of Distribution

- Drug pK_a .
- Extent of drug-plasma protein binding.
- Partition coefficient of the drug in fat (lipid solubility).
- V_d may be affected by:
- **Patient's gender**
- **Patient's age:** Differences in distribution pattern of a drug in different age groups are mainly due to differences in
 - Total body water (both intracellular and extracellular) – is much greater in infants.
 - Fat content – is also higher in infants and elderly.
 - Skeletal muscles – are lesser in infants and in elderly.

- **Organ composition:** The blood brain barrier is poorly developed in infants, the myelin content is low and cerebral blood flow is high, hence greater penetration of drugs in the brain.
 - **Plasma protein content:** Low albumin content in both infants and in elderly.
 - **Pregnancy:** During pregnancy, the growth of uterus, placenta and fetus increases the volume available for distribution of drugs. The fetus represents a separate compartment in which a drug can distribute. The plasma and the extracellular fluid volume also increase but there is a fall in albumin content.
 - **Obesity:** In obese persons, the high adipose tissue content can take up a large fraction of lipophilic drug despite the fact that perfusion through it is low. The high fatty acid levels in obese persons alter the binding characteristics of acidic drugs.
 - **Diet:** A diet high in fats will increase drugs such as NSAIDs to albumin.
 - **Disease states:** A number of mechanisms may be involved in the alteration of drug distribution characteristics in disease states:
 - Altered albumin and other drug-binding protein concentration.
 - Altered or reduced perfusion to organs or tissues.
 - Altered tissue pH.
- Example:** An interesting example of altered permeability of the physiologic barrier is that of blood brain barrier (BBB). In meningitis and encephalitis, the BBB becomes more permeable and thus polar antibiotics such as penicillin G and ampicillin which do not normally cross it, gain access to the brain.
- **Drug interactions:** Drug interactions that affect distribution are mainly due to differences in plasma protein or tissue binding of drugs.

2.7 METABOLISM OF DRUGS

"Enzymatic modification of the drug occurring within the living organisms or chemical transformation a drug goes through in living organisms or biological fluids is known as Metabolism or biotransformation".

Biotransformation occurs in those foreign agents to whom the body is exposed, which may be for therapeutic, intentional, unintentional or recreational purposes. Once these agents gain entry, they undergo chemical reactions or remain inert. Whenever these drug molecules are administered, pharmacokinetic process occurs, first absorption sets into play, then distribution, metabolism and finally elimination takes place.

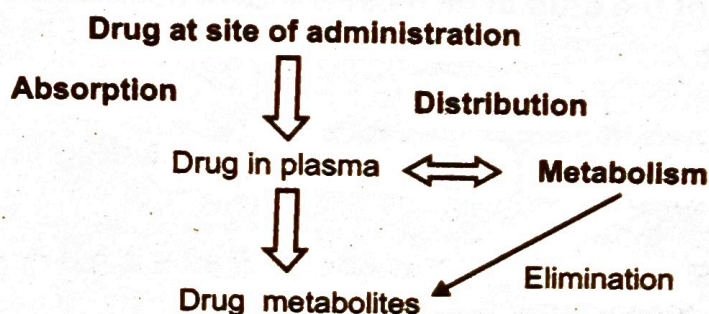


Fig. 2.10: Metabolism of drug

Biotransformation occurs only for the agents at physiological pH, having low molecular weight and fewer complexes. Highly lipophilic, non-ionized, high molecular weight or agents complexed with tissue or plasma proteins are not biotransformed easily. Biotransformation is a process specifically to make agents more polar and excretable. If biotransformation does not occur, drugs may have longer duration of action, and undesired effects are observed along with desired ones. Biotransformation, in fact, is the inactivation of pharmacological action of drugs. Biotransformation may convert drugs to active metabolites or inactive sometimes toxic metabolized products.

Drug Biotransformation Sites: Liver is the main organ. Others include GIT, lungs, kidneys, skin, adrenals and blood (plasma). Some of the drugs biotransformed at these sites include:

- **Liver:** Meperidine, pentazocine, morphine, nitroglycerine, lidocaine, propranolol, paracetamol, prazosin.
- **GIT:** Insulin, catecholamines, clonazepam, chlorpromazine, tyramine, salbutamol.
- **Lung:** Prostanoids.
- **Plasma:** Suxamethonium.

Types of Biotransformation:

1. Enzymatic

- (a) Microsomal
- (b) Non-microsomal

2. Non-enzymatic (Hofmann Elimination).

1. Enzymatic Elimination:

Biotransformation taking place due to different enzymes present in the body/cells is known as enzymatic elimination.

(a) Microsomal Biotransformation: Enzymes responsible are present within the lipophilic membranes of endoplasmic reticulum. After isolation and putting through homogenization and fractionation, small vesicles are obtained, known as microsomes. They possess all functional, morphological properties of endoplasmic reticulum i.e. smooth and rough. Smooth ER is concerned with biotransformation and contains enzyme components while the rough ER is mainly concerned with protein synthesis. Enzymes isolated from ER possess enzymatic activity termed as **microsomal mixed function oxidase system**.

Components:

- Cytochrome P450 (ferric, ferrous forms).
- NADPH (flavoprotein).
- Molecular oxygen.
- Membrane lipids.

Cytochrome P450: Cytochromes are the heme proteins, present abundantly within the living kingdom. They have about thousand known kinds. Only 50 of these heme proteins are found within the humans, which are divided into 17 families and sub-families. Name is derived because it is a heme protein (abbreviation cyp) and 450 because it reacts with carbon monoxide and during the reaction absorbs light at 450 nm.

NADPH: NADPH is a flavoprotein, less abundant than cyp450. For every 10 molecules of cytochrome P450, only one NADPH cytochrome reductase is present.

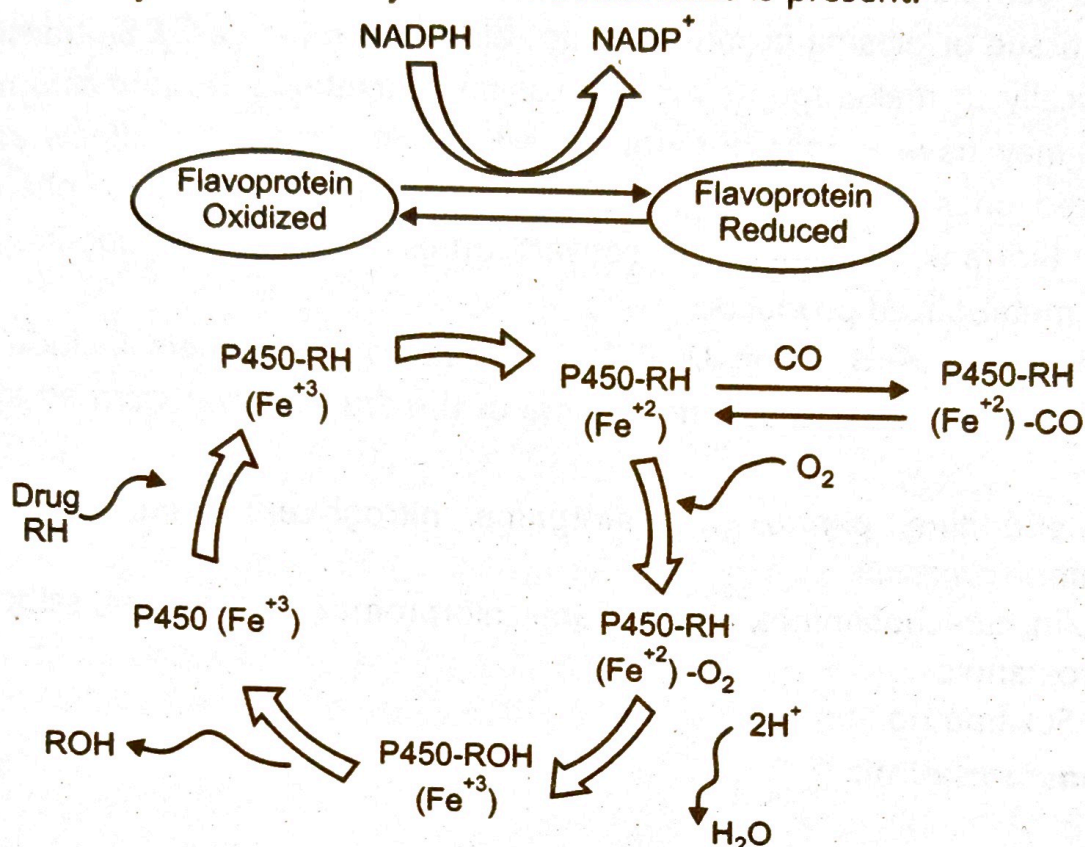


Fig. 2.11: Cytochrome P450 cycle, RH is parent drug, ROH is oxidized metabolite, e⁻ is electron

(b) Non-Microsomal Biotransformation: The type of biotransformation in which the enzymes taking part are soluble and present within the mitochondria.

Examples include:

- Xanthine oxidase converting hypoxanthine into xanthine.
- Cytotoxic agent 6-mercaptopurine.
- Monoamine oxidase involved in non-microsomal metabolism of catecholamines and noradrenaline.
- Alcohol dehydrogenase responsible for metabolism of ethanol into acetaldehyde.
- Tyrosine hydrolases enzymes.

2. Non-Enzymatic Elimination:

Spontaneous, non-catalyzed and non-enzymatic type of biotransformation for highly active, unstable compounds taking place at physiological pH. Very few drugs undergo non-enzymatic elimination.

Some of these include:

- Mustin HCl converted into Ethyleneimonium.
- Atracurium converted into Laudanosine and Quaternary acid.
- Hexamine converted into Formaldehyde.
- Chlorazepate converted into Desmethyl diazepam.

Biochemical Reactions:

1. Phase I reactions.
2. Phase II reactions.

1. Phase I reactions:

Phase I reactions are non-synthetic catabolic type of chemical reactions occurring mainly within the ER. They are the reactions in which the parent drug is converted into more soluble excretable agents by introduction or unmasking of functional component.

Example includes phenobarbitone, aromatic hydroxylation of which abolishes its hypnotic activity. Similarly, metabolism of azathioprine produces 6-mercaptopurine.

Drug products, which are water soluble, are excreted by the kidneys. Sometimes this is not true and phase I compounds do not result in true inactivation and may act as functional components of phase II reactions.

Phase I reactions include:

- Oxidation
- Reduction
- Hydrolysis

Oxidation: Reactions resulting in the addition of oxygen and/or the removal of hydrogen:

- $R-H \rightarrow R-OH$ (hydroxylation): Conversion of a hydrogen to a hydroxyl group.
- $R-C-OH \rightarrow R-C=O$ (dehydrogenation): Conversion of a hydroxyl group to a carbonyl group.
- $R-C=O \rightarrow R-COOH$ (carboxylation): Conversion of a carbonyl group to a carboxyl group.
- $R-C-NH_2 \rightarrow R-C=O$ (deamination): Conversion of an amino group to a carbonyl group.
- $R-CH_3 \rightarrow R-H$ (demethylation): Conversion of a methyl group to hydrogen.

An example of an oxidation reaction is the hydroxylation of amphetamine to 4-hydroxyamphetamine and norephedrine. Another example is hydroxylation of delta-9-THC to 11-OH-delta-9-THC. The enzymes of oxidation include mixed-function oxidases, monooxygenases, and cytochrome P450 enzymes.

Types of reactions performed by the Cytochrome P450 system:

- Aromatic hydroxylation : Phenobarbital, amphetamine.
- Aliphatic hydroxylation : Ibuprofen, cyclosporine.
- Epoxidation : Benzo [a] pyrene.
- N-Dealkylation : Diazepam.
- O-Dealkylation : Codeine.
- S-Dealkylation : 6-Methylthiopurine
- Oxidative Deamination : Diazepam, amphetamine.

- N-Oxidation : Chlorpheniramine.
- S-Oxidation : Chlorpromazine, cimetidine.
- Phosphothionate oxidation : Parathion.
- Dehalogenation : Halothane.
- Alcohol oxidation : Ethanol.

Reduction: Reactions resulting in the addition of hydrogen and/or the removal of oxygen:

- $R-OH \rightarrow R-H$ (dehydroxylation).
- $R-C=O \rightarrow R-C-OH$ (hydrogenation).
- $R-COOH \rightarrow R-C=O$ (decarboxylation).
- $R-NO_2 \rightarrow R-NH_2$ (amination).
- $R-C-H \rightarrow R-CH_3$ (methylation).

An example of a reduction reaction is the inactivation of warfarin by the transformation of a ketone group to a hydroxyl group (hydrogenation). Enzymes involved in reduction reactions are called reductases.

Hydrolysis: In a reaction with water, a bond in the compound is broken, resulting in two compounds. At the same time the water molecule splits into two, with hydrogen transferring to one of the compounds and a hydroxide to the other compound.

- $R-COO-R' + H_2O \rightarrow R-COOH + R'-OH$
- $R-CO-NH-R' + H_2O \rightarrow R-COOH + R'-NH_2$

The conversion of cocaine to benzoylecognine and ecognine methyl ester are examples of hydrolysis reactions. The enzymes of hydrolysis reactions include esterases, peptidases, and amidases.

Consequences of Phase I reactions:

- Active drug may be converted into inactive metabolite. Active parent drug inactivation may terminate biological activity.
- Active drug may be converted into active metabolite. E.g. morphine is converted into more active metabolite.
- Prodrug may be converted into active metabolite
- Active drug may be converted into toxic metabolite e.g. halothane used in general anesthesia, is converted into trifluoroacetylated compound or trifluoroacetic acid, leading to hepatic toxicity.
- Biotransformation of xenobiotics to mutagenic or carcinogenic agents.
- Conversion of xenobiotics into harmless compound.

Phase II reactions: Phase I metabolites if not readily excretable or contain component ends, combine with endogenous substrates like glucuronic acid, sulphuric acid, amino acid or acetic acid, to undergo conjugation reactions, yielding more excretable drug conjugates which are excreted by the kidneys. Phase II reactions are said to be **synthetic**, occurring within **cytosol**, while some occur within mitochondria.

Phase II reactions includes

- Glucouronidation.
- Sulfation.
- Acetylation.
- Methylation.
- Conjugation with glutathione.
- Conjugation with amino acids e.g. taurine, glutamine, glycine

Table 2.4: Some Phase II Reactions

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyl transferase (microsomal)	Phenols, Alcohols, Carboxylic acids, Hydroxylamine, Sulfonamides	Morphine, Acetaminophen, Diazepam, Digitoxin, Digoxin, Meprobamate
Acetylation	Acetyl-CoA	N-Acetyl transferase (cytosol)	Amines	Sulfonamides, Isoniazid, Clonazepam, Dapsone, Mescaline
Glutathione conjugation	glutathione	GSH-S-transferase (cytosolic, microsomes)	Epoxides, Nitro groups, Hydroxylamines	Ethycrinic Acid, Bromobenzene
Sulfate conjugation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, Alcohols, Aromatic amines	Estrone, 3-Hydroxy Coumarin, Acetaminophen, Methylidopa
Methylation	S-Adenosyl-methionine	Transmethylases (cytosol)	Catecholamines, Phenols, Amines, Histamine	Dopamine, Epinephrine, Histamine, Thiouracil, Pyridine

Phase II reactions lead to:

- Usually inactivation of drug.
- Production of water soluble metabolites, which is the main aim of biotransformation.

- Usually detoxification reaction for xenobiotics (as some substances might be carcinogenic).
- There are some important exception, toxic metabolites may be produced by their activation, e.g. methanol is converted into formaldehyde, which is toxic.
- Certain conjugation reactions may lead to the formation of reactive species responsible for the hepatotoxicity of drugs.
- Products produced might be more potent e.g. M-6-P.
- Reactions are mainly conjugate reactions. Normally phase I reactions are followed by phase II reactions but in case of **isoniazid** (antituberculous drug), phase II reactions occur before phase I reactions because N-acetyl moiety acts as an endogenous substrate for the conjugation reaction. This is followed by phase I hydrolysis to isonicotinic acid.

Effects of Phase II reactions on drugs:

- Lipid solubility is totally converted into solubility.
- Drugs are generally inactivated.
- Sometimes drugs are activated e.g. minoxidil is activated to minoxidil-o-sulphate (a vasodilator). Morphine is activated to morphine-6-glucuronide.

2. Phase III reactions:

Some reactions coupled with excretory pumps in the cell membranes are known as phase III reactions. Drugs undergoing these reactions are still the subject of extensive research even today.

2.7.1 Factors Affecting Biotransformation

Biotransformation is significantly affected by a number of factors, these include:

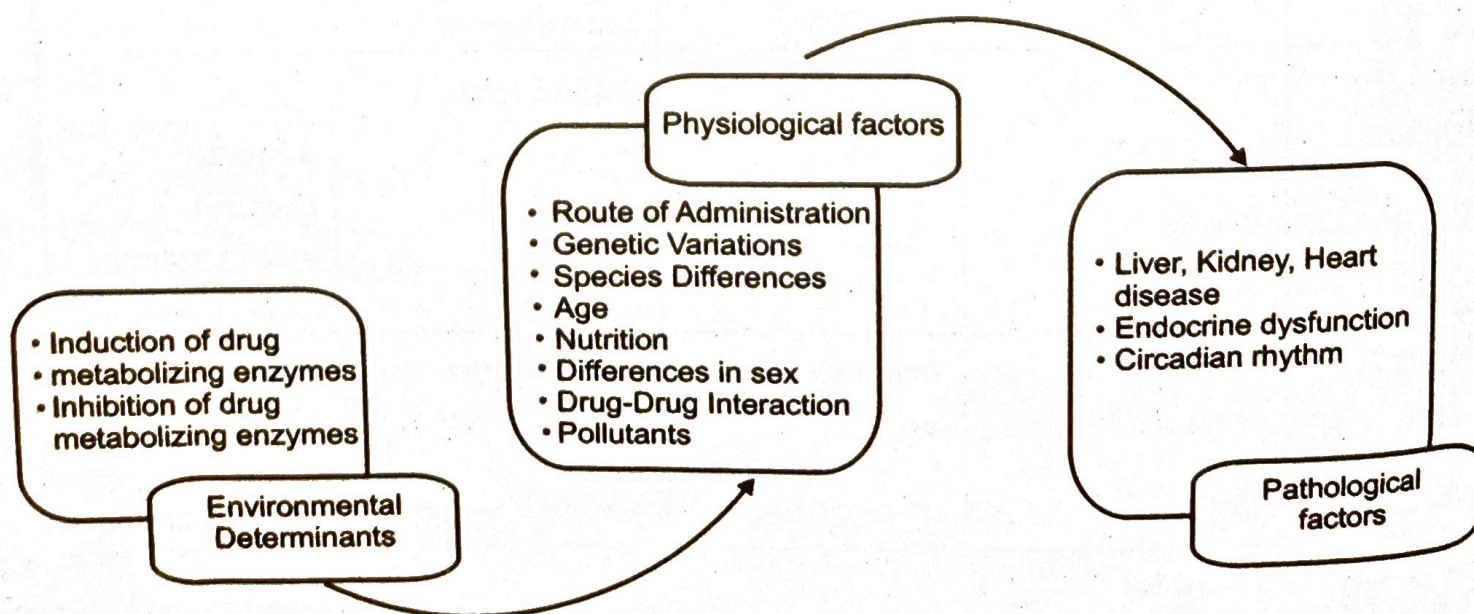


Fig. 2.12: Factors affecting metabolism of Drug or Biotransformation of Drug

(A) Environmental Determinants:**1. Enzyme Induction:**

When drugs given over prolonged period of time, up regulation of enzymes takes place. Most of the time cytochrome P450 is involved leading to increased synthesis of new enzymes. The rate of metabolism increases as enzyme induction takes place. The drugs which bring about these changes are known as enzyme inducers. Some examples include anticonvulsants like phenytoin, carbomycin and chronic alcoholism. Others include various sedatives, hypnotics, tranquilizers and insecticides.

When drugs are taken together, sometimes drugs acting as enzyme inducers for others cause increased metabolism of themselves, which is known as autometabolism. Example includes Artemether and carbamazepine when taken together. Enzyme induction is brought about by gene transcription, which is enhanced. Enzyme induction leads to a decreased levels of the parent drug and increased levels of metabolites. Sometimes toxic metabolites are also produced. The rate of reaction increases and quicker conversion of parent drug takes place. Drugs following first pass metabolism, have decreased bioavailability.

Significance: Care should be taken when enzyme inducers are given, especially when two drugs are given together, drug-drug interaction might occur, leading to therapeutic failure.

- Rifampicin is an enzyme inducer. If it is taken by female patients using contraceptives, decreased therapeutic effect might occur, leading to pregnancy. Therefore, the dose should be increased.
- Phenobarbitone is used in seizures and epilepsy. It is also an enzyme inducer. If it is administered to patients taking warfarin, therapeutic failure might occur, leading to increased bleeding tendency.

Some enzyme inducers include:

- Ethchlorvynol enhances metabolites of warfarin.
- Phenytoin enhances metabolism of cortisol and digitoxin.
- Rifampicin increases metabolism of digitoxin.
- Barbiturates.
- Chloral hydrate.
- Erythromycin.

Drugs which are significantly affected by enzyme induction include:

- | | |
|-----------------------|-------------------|
| • Phenytoin | • Warfarin |
| • Tolbutamide | • Imipramine |
| • Oral contraceptives | • Chloramphenicol |
| • Doxycycline | • Theophylline |
| • Griseofulvin | • Phenylbutazone |

Consequences of Microsomal Enzyme Induction

1. Decreased intensity and duration of action of drugs e.g. failure of contraceptives.
2. Increased intensity of action of drugs activated by metabolism. E.g. acute paracetamol toxicity is due to one of its metabolites.

3. If drug induces its own metabolism e.g. cicobarbitone it develops tolerance so effects are not produced.
4. Precipitation of acute intermittent porphyria. Enzyme induction might increase porphyrin synthesis.
5. Intermittent use of an inducer might interfere adjustment of dose of another drug e.g. oral anti-coagulants, oral hypoglycemic, antiepileptics and antihypertensive.

Auto induction: The phenomenon in which a drug induces metabolism of other drugs as well as its own. E.g. carbamazepine-antiepileptic.

2. Enzyme Inhibition:

The process in which drug metabolizing capacity of cytochrome is decreased is known as enzyme inhibition. The rate of metabolism is decreased. Drugs bringing about these changes are known as enzyme inhibitors. Examples include ketoconazole- antifungal drug, cimetidine and verapamil- calcium channel blocker.

Enzyme inhibition is a rapidly occurring process, most critical for the drugs having a large therapeutic index. Competition for the active sites takes place between the enzymes and the given drugs. When enzyme inhibitor attaches, less metabolism occurs. As rate of metabolism is decreased, plasma levels of parent drug are increased while those of metabolites are low. Serious drug-drug interactions might occur, as the plasma half life is also increased.

Sulfonamides decrease the metabolism of phenytoin so that its blood levels become toxic. Cimetidine decreases the metabolism of propranolol leading to enhanced bradycardia. Metabolism of tolbutamide is inhibited by phenylbutazone or coumarins, leading to prolonged hypoglycemia. Oral contraceptives inhibit metabolism of antipyrine.

(B) Physiological Factors:

1. **Presystemic Metabolism/First pass effect/Route of Administration:** Drugs following first pass metabolism have decreased bioavailability. Most of the drugs are metabolized within the liver. Changing the route of administration might change the first pass metabolism. Propranolol is 80% metabolized before reaching systemic circulation.
2. **Genetic Variations:** Inter individual variations might occur, as drugs behave differently in different individuals due to genetic variations resulting in absent or malformed enzymes due to absent or malformed genes. Mostly non-microsomal enzyme show genetic variations. Examples include succinyl choline, which is a skeletal muscle relaxant. It is metabolized by pseudocholine esterase. Some people lack this enzyme, due to which lack of metabolism of succinyl choline might occur. When administered in those individuals, prolonged apnea might result. Different groups of populations might be classified as fast metabolizers and poor metabolizers of drugs. For certain drugs, like isoniazid, fast acetylators as well as slow acetylators are present. Fast acetylators cause rapid acetylation, while poor

metabolizers metabolize less. Hepatic acetyl transferrase catalyzes acetylation. Slow acetylation might occur due to genetic malformation leading to decreased production. Fast metabolism may lead to hepatotoxicity while poor metabolism might result in peripheral neuropathy. Absence of catalase may lead to achalasia, while G6PD deficiency predisposes erythrocytes to hemolysis as a result of oxidative stress imposed by some commonly used drugs.

3. **Species Differences:** Species differences are most established in animals. Some metabolize drugs rapidly. Rats and rabbits metabolize drugs more efficiently than humans. Certain species of rabbits feed on Belladonna, and have atropinase to tolerate the effects of atropine. Research on humans is still going on. Asians, Orientals, blacks and whites might have different drug metabolizing capacity. Examples include difference in drug metabolizing capacity of certain anti-malarial, amongst the Eskimos and the Asians. Eskimos may metabolize drugs more efficiently than the Asians.
4. **Exposure to Pollutants from Environment or Industry:** Cigarette smokers might act as enzyme inducers. Chronic alcoholism might lead to enzyme induction as well. Similarly, pesticides or insecticides may act as enzyme inducers. In hot and humid climate biotransformation is decreased and vice versa. At high altitude, decreased biotransformation occurs due to decreased oxygen leading to decreased oxidation of drugs.
5. **Age:** Age plays a very important role. Extreme age groups (very young and very old) behave almost the same. Drug metabolizing enzyme develop early but their capacity is low. Thus, the rate of metabolism in an infant is very low. Care should be taken in administering drugs in younger patients. True development of enzyme occurs in one to two months.
 - Chloramphenicol (antimicrobial drug) when administered in infant, does not have great efficacy. Toxic effects in the form of grey baby syndrome might occur. The baby may be cyanosed, hypothermic, flaccid and grey in colour. Shock and even death might occur if toxic levels get accumulated.
 - Diazepam (sedative hypnotic) may result in floppy baby syndrome in which flaccidity of the baby is seen.
 - In elderly, most processes slow down which leads to decreased metabolism. Shrinkage of organs occurs as well along with decreased liver functions and decreased blood flow through the liver. All these factors decrease the metabolism. Old people are usually taking multiple drugs, so are more prone. The drug doses should be decreased in the elderly.
6. **Sex:** Males have a higher BMR as compared to the females, thus can metabolize drugs more efficiently, e.g. salicylates (others might include ethanol, propanolol, benzodiazepines). Females, during pregnancy, have an increased rate of metabolism.

Thus, the drug dose has to be increased. After the pregnancy is over, the dosage is decreased back to normal levels. Example includes phenytoin, whose dose has to be increased during pregnancy (specially second and third trimester).

7. **Drug-Drug Interaction:** Toxic effects might result when drug combinations act as enzyme inhibitors and inducers. The dose has to be adjusted accordingly.
8. **Nutrition:** Malnutrition may also affect biotransformation. Depletion of amino acids and glycine may affect drug metabolizing capacity, especially during the phase II, which depends on the food stores. Synthesis of microsomal enzymes depends on nutritional status.

C. Pathological Factors:

1. **Disease Conditions:** Most of the drugs are metabolized in the liver, any disease of which (cirrhosis, viral hepatitis, drugs induced hepatitis, hepatocarcinoma) may affect and slow down the metabolizing capacity.

- Jaundice depresses glucuronic acid conjugation and oxidative function of liver microsomes.
 - Cardiovascular diseases, although have no direct effect, decrease the blood flow, which may slow down biotransformation of drugs like isoniazid, morphine and propranolol.
 - Similarly pulmonary conditions may decrease biotransformation. Procaine and procainamide hydrolysis is impaired.
 - Hormonal diseases, infections and inflammation can change drug metabolizing capacity.
 - Hypothyroidism increases drug metabolizing capacity (increased half-life of antipyrine, digoxin, methimazole, practolol) while hyperthyroidism decreases it.
2. **Circadian rhythm:** The rate of hepatic metabolism of certain drugs follow diurnal rhythm in rats and mice. This may be true in humans as well.

2.7.2 Prodrugs

Prodrugs contain parent drug compounds in inactive form. Active specie is required to be carried to the site of action. Prodrugs carry maximum amount of specie to site of action. These prodrugs have minimum biological activity, longer half-life and low toxic activity. They undergo biotransformation to bring about desired results.

Advantages of Prodrugs:

1. More stable.
2. Better bioavailability.
3. Low side effects.
4. Less toxic.
5. Desirable pharmacokinetic profile.
6. Increase concentration of drug at site of action.
7. Increase duration of action of drug.

Examples:

1. Chloral hydrate converted into trichloroethanol.
2. Phenacetin converted into paracetamol.
3. 6-metacaptoprine.
4. Cortisone converted into hydrocortisone.
5. Prednisone converted into prednisolone.
6. Clorazepate.
7. Dipivefrin.
8. Enalapril converted into enalaprilat.

2.8 EXCRETION OF DRUG

Drug excretion is the process of eliminating a drug from the body. A drug, which is either biologically active itself or a prodrug, may be excreted in its original chemical state. Alternatively, all or a portion of a drug may undergo chemical modification and be eliminated as biologically active, or inactive, metabolites (see the record on Drug Biotransformation). There are several routes for drug elimination from the body. The majority of drugs are eliminated by pathways that involve the kidneys or the liver.

When drugs are taken in, they should be eliminated as well, as we do not want their action to continue indefinitely. If they remain in the body, they might produce undesirable results. Excretion and clearance are two separate terms but are closely linked together.

Drugs can be excreted into two forms:

1. Unchanged drugs.
2. Form of metabolites.

The primary role of biotransformation is to convert lipophilic drugs into hydrophobic compounds or to convert non-excretable drugs into excretable forms. Being lipophilic is a property desirable for absorption and passage through the body, but not for excretion.

Major	Kidney Filtration Secretion Reabsorption	Liver Metabolism Secretion
	Lungs Exhalation	Others Saliva, Tears, Milk of Mother, Hair, Skin, etc.
		Minor

Fig. 2.13: Sites for Excretion

Renal Excretion: The kidney is the principal drug-excreting organ. The three components of renal excretion, i.e. glomerular filtration, secretion, and reabsorption. The first two processes remove drugs from plasma, whereas the third process retains drugs in the body by returning them to plasma. The net excretion of the drug, therefore, depends on the sum total of three processes.

1. **Glomerular filtration:** Unbound drug molecules of less than 20000 Da are filtered through the glomerulus with the primary urine.
2. **Active tubular secretion:** This mechanism is predominant in the proximal tubule. Several transporters are responsible for the tubular secretion of drugs: the P-glycoproteins (PGPs), the multidrug resistance associated proteins (MRPs), the organic anion transporters (OATs), the organic cation transporters (OCTs), etc. These transporters are not highly specific and may become saturated at high drug concentrations.
3. **Tubular reabsorption:** This process is helpful for non-ionized form of the drug is able to diffuse across the tubular membrane and reenter the plasma.

Factors influencing renal drug excretion:

- **Gender:** Renal excretion is 10% lower in female than in males.
- **Age:** Renal function decrease 50% with age (25-75 years).
- **Pregnancy:** Renal function increase 50% in pregnancy.
- **Disease:** In Renal disease, heart failure the renal drug excretion is reduced due to decrease renal blood flow.
- **Molecular Weight:** Drugs with Molecular weight <300, water soluble are excreted in kidney. Molecular weight 300 to 500 are excreted both through urine and bile. The larger the chemical, the more difficulty in passing through a cell membrane even if it is lipid soluble.
- **Binding characteristics of the drug:** Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. Only unbound or free drug appear in glomerular filtrate. Protein bound drug has long half-lives.
- **pH:** pH influences the degree of Ionisation of weakly acidic and weakly basic drugs. Changes in Urinary pH can result in 'Ion-trapping', reducing reabsorption in the distal tubule. Forced alkaline diuresis for treatment of Salicylate overdose - administration of IV sodium bicarbonate promotes renal elimination. Unionized aspirin, filtered by kidney, becomes ionized in alkalized urinary filtrate, which reduces its reabsorption.
- **Drug Interaction:** Drug-drug interaction either increases or decreases drug excretion by renal.
 - Salicylates block uricosuric action of probenecid and sulfinpyrazone and decrease tubular secretion of methotrexate.
 - Probenecid decreases the concentration of nitrofurantoin in urine, increases the duration of action of penicillin/ampicillin and impairs secretion of methotrexate.
 - Sulfinpyrazone inhibits excretion of tolbutamide.
 - Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier P-gp.

Non-renal routes of drug excretion:

1. Biliary excretion.
2. Pulmonary excretion.
3. Excretion via. Breast milk.
4. Sweat elimination.
5. Salivary excretion.

Biliary Excretion: Excretion in the bile is a relatively minor route of elimination of unmetabolized drugs, but it is a major route of elimination of drug metabolites, particularly water-soluble conjugates. Drugs are actively secreted in the bile, and passed into the intestines, from where they may be either reabsorbed or lost in the faeces. Drugs that are unabsorbed from the gut, or secreted into the gastrointestinal tract by the bile, salivary glands and digestive glands are excreted in the faeces.

Pulmonary Excretion: This route of excretion is important primarily for gaseous and volatile liquid general anesthetics, which can be excreted from the bloodstream across the alveolar membrane into the expired air. Excretion of drugs in sweat, saliva, milk and gastric juice is mainly by passive diffusion of non-ionized form. Some drugs are transferred to the suckling infant in breast milk in significant amounts. Hence, drug use by breastfeeding mother should be restricted to the minimum.

Excretion via Breast Milk: Breast milk is a quantitatively relatively minor route of drug excretion. Nevertheless, it is clinically important for breastfeeding mothers and their infants. The baby will ingest drugs excreted in the breast milk. Moreover, breast milk has a lower pH than plasma. Accordingly, basic drugs will be concentrated in the breast milk through the phenomenon of ion (pH) trapping.

Sweat elimination: Sweat can contain traces of compounds such as iodine, bromine, ethanol, salicylic acid, sulphamides and various trace elements. But the sweat elimination appears secondary compared to the renal, hepatic and pulmonary elimination.

Salivary Excretion: The pH of saliva varies from 5.8 to 8.4; hence it is helpful for excretion of non-ionized lipid soluble drugs like Iodine, Metronidazole, Lithium, Phenytoin, Caffeine, and Theophylline.

2.9 KINETIC ELIMINATION OF DRUG

The irreversible shift of a drug from one part of the body to other part of system is known as elimination. It is from the more perfused parts to the lesser perfused parts. Elimination may be by:

1. Biotransformation
2. Excretion

Types of Elimination Kinetics:

First-order kinetics: "Elimination of a constant fraction per time unit of the drug quantity present in the organism. The elimination is proportional to the drug concentration." For most drugs, the elimination occurs at a rate directly proportional to the concentration of the drug—i.e., the higher the drug concentration, the higher its elimination rate (e.g., 50% per unit time, as shown in the Fig. 2.11). First-order kinetics is also referred to as non-saturable or linear kinetics.

Zero-order kinetics: "Elimination of a constant quantity per time unit of the drug quantity present in the organism." With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, the plasma drug concentration is much greater than the

Michaelis constant K_m , and drug metabolism is constant and independent of the dose. Zero-order kinetics is also known as saturable, dose- or concentration independent or nonlinear kinetics.

Half-Life: Half-life ($t_{1/2}$) is the time required to reduce the amount of drug in the body by 50%. Thus, after two half-lives, 25% of the drug is left; after three, 12.5%; and after 4 half-lives, 6.25%. The half-life determines the length of the drug's effect. However, it is not the only factor, as simply calculating half-life assumes the body to be a single compartment. In reality, drugs exhibit multi-compartment pharmacokinetics (i.e., distribution in different tissue and fluid spaces), which affects the "true" half-life (see the volume of distribution below).

Bioavailability: Fraction of the dose of a drug contained in any dosage form that reaches the systemic circulation in unchanged or active form administered through any route is known as bioavailability. Drugs injected using intravenous route of administration have 100% bioavailability, while others have much less bioavailability, because:

- Extent of absorption
- First-pass metabolism
- Volume of distribution

$$\text{Bioavailability} = \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

or

$$\text{Bioavailability} = \frac{\text{AUC (oral)}}{\text{AUC (IV)}} \times 100$$

Where, AUC is the area under the curve.

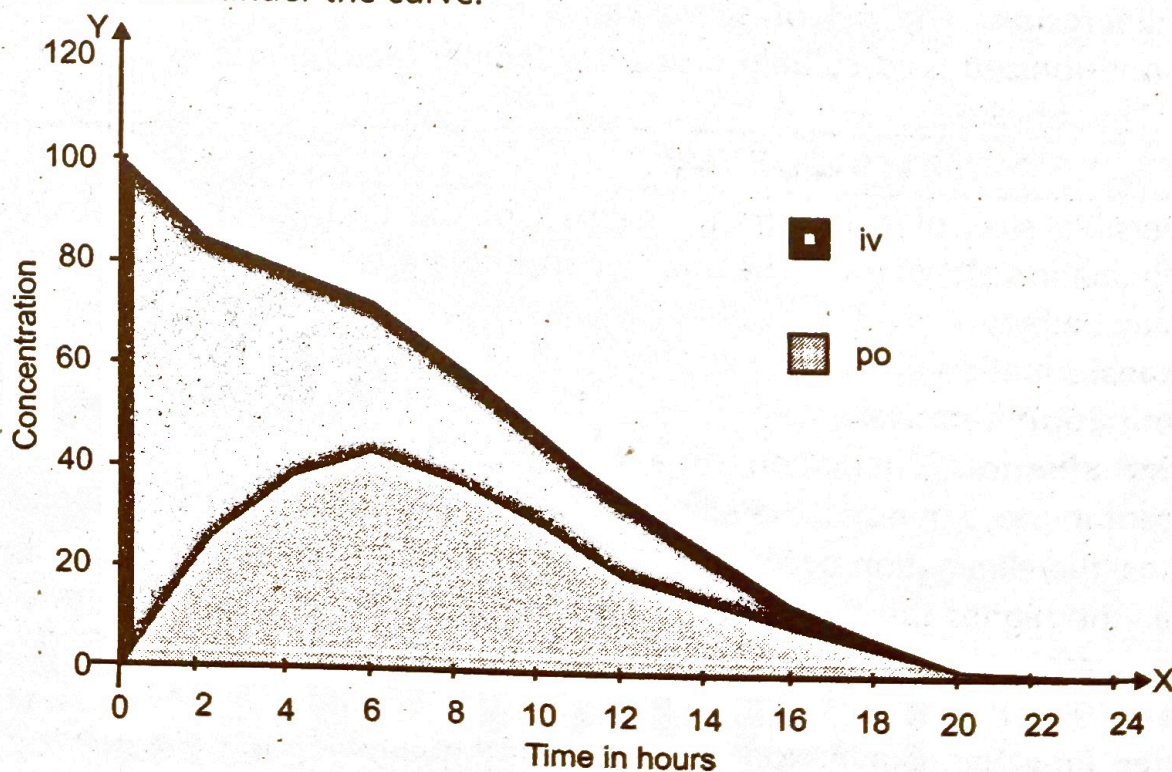


Fig. 2.14: Comparison of Bioavailability between intravenous and oral route administration of drug

X-axis represents time, while y-axis represents the plasma concentration. Bioavailability is the ratio of the area calculated for oral route of administration to the intravenous route of administration. It is determined by comparing the plasma levels of a drug after administration with plasma drug level achieved by IV injection.

Bioavailability differs not only among drugs and routes of administration, but also between different formulations of the same drug. When two drug formulations have similar bioavailability, they are said to be **bioequivalent**.

Drugs having 100% bioavailability include chlordiazepoxide, diazepam, lithium, metronidazole, phenobarbitol, salicylic acid, trimethoprim and valproic acid.

Relative bioavailability: Whenever the bioavailability of an oral drug (for example tablet) is compared with other oral formulation (for example: suspension) of same drug is known as relative bioavailability. Time course of drug plasma concentrations following the administration of different extravasal formulations; $t_{1/2}$ four hours:

1. **IR:** Immediate release oral.
2. **DR:** Delayed release (gastric resistant; lag-time 2 hours).
3. **CR:** Controlled release (flip-flop PK; absorption slower than elimination).
4. **TDS:** Transdermal system (zero-order input rate, lag-time 1 hour; patch removed after 12 hours). Note that AUC_{∞} after all administrations are identical by Alfie.

License: CC BY 3.0

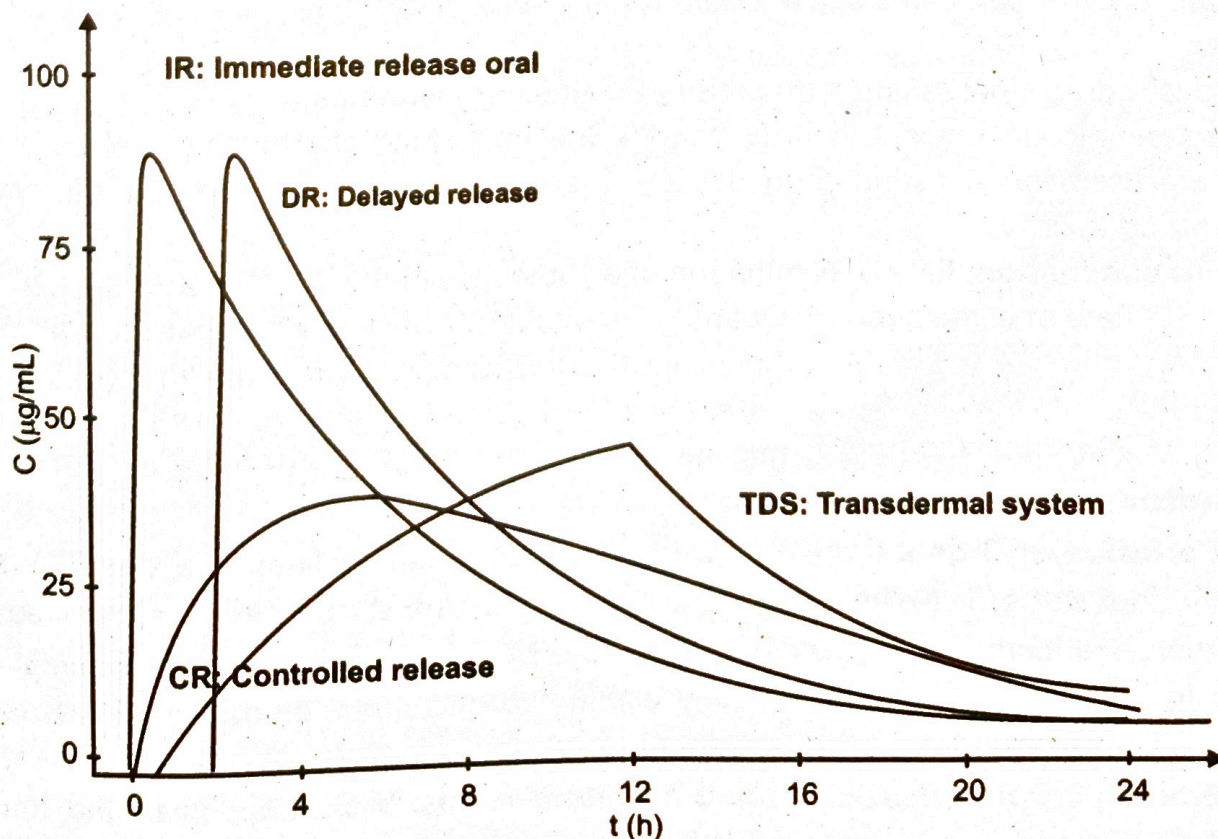


Fig. 2.15: Bioavailability of an oral drug (for example, tablet) is compared with other oral formulation (for example, suspension) of same drug

Therapeutic Index: Therapeutic index represents the safety of a drug. Drugs having large therapeutic index and safer and vice-versa.

$$\text{Therapeutic index} = \frac{LD50}{ED50} = \frac{TD50}{ED50^*}$$

Where, LD50 is a dose which can kill 50% of the animals administered.

ED50 is a dose which can save 50% of the animals.

TD50 is the median toxic dose.

ED50* is the median effective dose.

Drugs having low therapeutic index include: Anticonvulsants, lithium, anticoagulents, corticosteroids and cardio active drugs.

Therapeutic Window: Therapeutic window is the range between the high therapeutic index and low therapeutic index. Drugs with low therapeutic index have a narrow therapeutic window.

Clearance: Clearance (CL) of a drug is the rate of elimination of the drug from the body in relation to its plasma concentration. Elimination of a drug can occur at the kidneys, the liver, the lung, and/or other organs. Therefore, total systemic clearance (CL_{total}) will be a sum of clearances at all the relevant organs.

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

- Clearance is affected when there is an impairment in the function of the organ, e.g., hepatic disease can reduce the clearance (thereby prolonging the half-life) of many drugs.
- Obviously, drug kinetics and metabolism will affect its clearance.
- Total systemic clearance and drug half-life are important pharmacological parameters that are used for adjusting drug dosage, thereby enhancing therapeutic efficacy and minimizing toxicity.

Rate of elimination: Rate of elimination of a substance in urine is denoted by ROE.

$$\begin{aligned}\text{Rate of elimination} &= \text{Quantity or volume of urine measured (ml/min)} \times \\ &\quad \text{Concentration substances in urine (mg/ml)} \\ &= \text{ml/min} \times \text{mg/ml} \\ &= \text{mg/min}\end{aligned}$$

2.9.1 Factors affecting Elimination

1. **Perfusion of Organ:** If the drug is rapidly or completely eliminated, then the rate of blood flow does not affect elimination. E.g. mannitol is almost completely eliminated from kidneys; therefore increasing the blood flow to the kidneys has no effect on elimination of mannitol. In cases of drugs not completely eliminated, increased blood flow increases the rate of elimination.

2. **Binding to proteins/Bound and unbound forms:** If a drug is in bound form, its elimination is less and vice-versa.

3. **Metabolism:** Increased metabolism means decreased plasma half-life and increased elimination.

4. Clearance: Dopamine and prostaglandins cause vasodilatation of renal vessels, increasing their elimination. Adrenaline causes vasoconstriction, leading to decreased blood flow and decreased elimination. Renin is another vasoconstrictor.

Optimization of Dose: A drug should be administered in such a dose that maximizes the therapeutic efficacy and minimizes toxicity. The range of dose between low efficacy and high toxicity is called the therapeutic window. Thus, the target concentration of a drug (within the therapeutic window) can be calculated by knowing the pharmacokinetics of the drug. If the drug has a narrow therapeutic window (e.g., warfarin and digoxin), extra care is needed in the administration and drug levels may need to be monitored.

Maintenance dose: Drugs are usually administered at a frequency that maintains the concentration of the drug at a steady state within the therapeutic window. If the pharmacokinetic properties are known, the maintenance dose (or dosing rate) can be calculated as follows:

$$\text{Dosing rate} = \frac{(\text{Target plasma concentration} \times \text{CL})}{F}$$

Where, F is the bioavailability; for drugs administered via the intravenous route, F is 1.2.

The maintenance dose of the same drug can also differ depending on the condition being treated. For instance, in the case of aspirin, a 300 mg dose is required to reduce pain, fever and inflammation; however, a 75 – 160 mg dose is enough if used for the prevention of cardiovascular events such as myocardial infarction and stroke.

Loading dose: When the time taken by a drug to reach the target steady state concentration is high (for example, in drugs with long half-life), a loading dose should be administered to raise the plasma concentration of the drug within the target range in a shorter time. This loading dose, which is higher than the maintenance dose, can be given as one (usual) or multiple (less common) doses, and it is followed by a maintenance dose to maintain the steady state concentration.

Dose Adjustment (for Renal Disease): The dose that is usually prescribed is based on an average patient. However, many individual factors can affect the target plasma concentration of the drug, which has to be tailored for the individual patient if optimal therapeutic efficacy is desired.

This adjustment is required if an organ that metabolizes (and eliminates) the drug has impairment of function. Drugs excreted by the renal route frequently require dose adjustment based on the renal function. This function of the kidneys in elimination drugs can be estimated by measuring the creatinine clearance.

Renal clearance is measuring using the **Cockcroft-Gault** equation as follows:

$$(140 - \text{age}) \times (\text{Weight in kg}) \times (0.85 \text{ if female}) \div 72 \times (\text{Creatinine concentration in mg/dl})$$

The factor of 0.85 is applied for females because women have lesser muscle mass than men, and therefore the creatinine production in women is 85% of that in men.

QUESTIONS

1. Define drug absorption.
2. Define drug distribution.
3. Define biotransformation
4. What is first pass metabolism?
5. What is drug excretion?
6. Enlist the non-renal route for drug excretion.
7. Define the terms enzyme induction and enzyme inhibition.
8. Enlist the phases of drug metabolism.
9. Enlist the various physiological barriers for drug distribution.
10. Define the terms biological half-life.
11. What is drug absorption? Write the mechanism of drug absorption.
12. What is drug absorption? Explain the factors affecting drug absorption.
13. What is drug distribution? Explain in detail blood brain barrier and placental barrier.
14. Explain in detail the various physiological barriers for drug distribution.
15. Explain the factors affecting drug distribution.
16. Define drug metabolism. Write in detail phase-I and Phase-II reaction with example.
17. Write the factors affecting drug metabolism.
18. Write in detail the mechanism of drug excretion.
19. Define non-renal drug excretion. Write in detail the mechanism of non-renal route of drug excretion.
20. Write the factors affecting drug excretion.
