4th Edition

# Essentials of Pharmacology for Dentistry

*Covering the latest curriculum*

KD Tripathi

JAYPEE

# *Essentials of Pharmacology for Dentistry*

**4th Edition**

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# Preface to the Fourth Edition

Pharmacology, the science of drugs (medicines), is a highly dynamic discipline with concepts and priority drugs changing rapidly. Its relevance to all health professionals (including dentists) cannot be over emphasized. Practice of dentistry utilizes drugs both as primary treatment modality, as well as facilitator of/adjuvant to dental procedures. Dentists routinely prescribe analgesics and antibiotics, apply antiseptics and other locally acting drugs, and inject local anaesthetics. Further, many dental patients could be receiving other medication that may have orodental implications, or may interact with drugs prescribed by the dentist. Occasionally, dentists have to manage a medical emergency which may arise during a dental procedure or in their clinic. As such, a broad knowledge of pharmacology along with focus on particular aspects is needed by the dentist. This book has been produced to specifically meet the above outlined needs.

The book is divided into three sections. The first describes the general pharmacological principles with which all professionals involved in drug therapy must be conversant. The second on systemic pharmacology presents a brief account of drugs acting on various organ systems and used in the treatment of common disorders affecting these systems, but are generally not prescribed by dentists. Each chapter is organised systematically. The opening sentence defines the class of drugs, followed by their classification presented in hierarchical chart form for better pictorial impression and easy remembrance. The 'prototype' approach has been adopted by describing the representative drug of the class followed by few salient features of the others. Matters particularly relevant to dental therapeutics have been highlighted. Wherever applicable, the implications in dentistry are prominently elaborated, e.g. drugs and diseases affecting postextraction haemostasis, dental procedures in patients on corticosteroid therapy or in diabetics, orodental complications of cancer chemotherapy and chronic alcoholism, etc.

The third section covers antimicrobials and other drugs which the dentists usually prescribe or administer themselves. However, the allocation of topics in sections two and three does not indicate water-tight distinction, which is impossible, but has been done with a view to focus attention on drugs that have greater relevance in dentistry. To mention a few, the application of analgesics and NSAIDs in dental pain, local anaesthetics for dental anaesthesia, role of each class of antimicrobials in orodental infections, prophylaxis of postextraction wound infection and endocarditis in patients at special risk are emphasized. Since dentists are constantly exposed to the risk of accidental HIV infection by sharp injury while performing dental procedures, the latest NACO recommended guidelines for prophylaxis of HIV infection are provided. Drugs and aids having specific application in dental disorders and in dental care, e.g. drugs for dental plaque, caries tooth, dentine sensitivity alongwith aids like dentifrices, bleaching agents, disclosing agents, etc. are described in a separate chapter, pointing out their role in current practice. Management of medical emergencies like fainting, hypoglycaemia, allergic/anaphylactic reaction, angina pectoris or myocardial infarction, asthmatic attack or seizures that may occur in a dental

office are outlined in another chapter, along with a list of medicines that should be kept in the emergency tray. The last chapter on drug interactions highlights those that may be encountered in dental practice. Care has been taken that the syllabus prescribed by the Dental Council of India is fully covered.

All chapters in the present edition have been thoroughly updated to include latest information and new drugs, while nonrelevant material has been deleted. Presentation and illustrations have been improved. Leading trade names and dosage forms of drugs generally prescribed by dentists are mentioned distinctively. Thus, the book is oriented to provide core and contemporary pharmacological knowledge which can be easily assimilated by dental students, as well as serve to help dental practitioners in treating orodental conditions.

I am thankful to readers of the earlier editions for their comments and suggestions which helped in preparing the present edition. The motivational influence of Shri J.P. Vij (Group Chairman), M/s Jaypee Brothers Medical Publishers, was crucial. The meticulous preparation of the manuscript by the staff of M/s Jaypee Brothers Medical Publishers is highly appreciated. The participation and cooperation of my wife is sincerely acknowledged.

Nov. 2020 **KD Tripathi**

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## Section I: General Pharmacological Principles



## Section II: Systemic Pharmacology

## Section III: Antimicrobials and Drugs Important in Dental Therapeutics

# List of Abbreviations

| | |
|---|---|
| Ang-I/II/III | Angiotensin I/II/III |
| AA | Amino acid |
| AB | Antibody |
| abc | ATP binding cassettee (trasporter) |
| AC | Adenylyl cyclase |
| ACE | Angiotensin II converting enzyme |
| ACh | Acetylcholine |
| AChE | Acetylcholinesterase |
| ACT | Artemisinin combination therapy |
| ACTH | Adrenocorticotropic hormone |
| AD | Alzheimer's disease |
| ADP | Adenosine diphosphate |
| Adr | Adrenaline |
| AF | Atrial fibrillation |
| AFl | Atrial flutter |
| AG | Antigen |
| AIDS | Acquired immunodeficiency syndrome |
| AIP | Aldosterone induced protein |
| ALA | Alanine |
| AMA | Antimicrobial agent |
| AMB | Amphotericin B |
| amp | Ampoule |
| AMP | Adenosine monophosphate |
| ANC | Acid neutralizing capacity |
| ANS | Autonomic nervous system |
| ANUG | Acute necrotizing ulcerative gingivitis |
| AP | Action potential |
| APD | Action potential duration |
| APF | Acidulated phosphate fluoride |
| aPTT | Activated partial thromboplastin time |
| ARB | Angiotensin receptor blocker |
| ARC | AIDS related complex |
| ART | Antiretroviral therapy |
| ARV | Antiretrovirus |
| 5-ASA | 5-Amino salicyclic acid |
| AT-III | Antithrombin III |
| ATP | Adenosine triphosphate |
| ATPase | Adenosine triphosphatase |
| A-V | Atrioventricular |
| AVP | Arginine vasopressin |
| AZT | Zidovudine |
| $B_{12}$ | Vitamin $B_{12}$ |
| BCRP | Breast cancer resistance protein |
| BD | Twice daily |
| BHP | Benign hypertrophy of prostate |
| BMD | Bone mineral density |
| BMR | Basal metabolic rate |
| BP | Blood pressure |
| BPN | Bisphosphonate |
| BSA | Body surface area |
| BuChE | Butyryl cholinesterase |
| BW | Body weight |
| BZD | Benzodiazepine |
| C-10 | Decamethonium |
| CA | Catecholamine |
| CaBP | Calcium binding protein |
| CAD | Coronary artery disease |
| CAM | Calmodulin |
| cAMP | 3', 5' Cyclic adenosine monophosphate |
| cap | Capsule |
| CAse | Carbonic anhydrase |
| CBS | Colloidal bismuth subcitrate |
| CCB | Calcium channel blocker |
| CD | Collecting duct |
| cGMP | 3', 5' Cyclic guanosine monophosphate |
| CGRP | Calcitonin gene-related peptide |
| CH | Cholesterol |
| ChE | Cholinesterase |
| CHE | Cholesterol ester |
| CHF | Congestive heart failure |
| CI | Cardiac index |
| CL | Clearance |
| CLcr | Creatinine clearance |
| Clo | Clofazimine |
| CMI | Cell-mediated immunity |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| c.o. | Cardiac output |
| CoEn-A | Coenzyme-A |
| COMT | Catechol-O-methyl transferase |
| COX | Cyclooxygenase |
| CPS | Complex partial seizures |
| CPZ | Chlorpromazine |
| CRF | Corticotropin releasing factor |
| CSF | Cerebrospinal fluid |
| CTZ | Chemoreceptor trigger zone |
| CVS | Cardiovascular system |
| CWD | Cell wall deficient |
| CYP450 | Cytochrome P450 |
| DA | Dopamine |
| DA-$B_{12}$ | Deoxyadenosyl cobalamin |
| DAG | Diacyl glycerol |
| DAT | Dopamine transporter |
| DCI | Dichloroisoproterenol |
| DDS | Diamino diphenyl sulfone (Dapsone) |
| DHFA | Dihydro folic acid |
| DHFRase | Dihydrofolate reductase |

| | |
|---|---|
| DHP | Dihydropyridine |
| DIT | Diiodotyrosine |
| dl | Decilitre |
| DLE | Disseminated lupus erythematosus |
| DMCM | Dimethoxyethyl-carbomethoxy-β-carboline |
| DMPA | Depot medroxyprogesterone acetate |
| DMPP | Dimethyl phenyl piperazinium |
| DNA | Deoxyribonucleic acid |
| DOCA | Desoxy corticosterone acetate |
| dopa | Dihydroxyphenyl alanine |
| DOSS | Dioctyl sulfosuccinate |
| DOTS | Directly observed treatment short course |
| DPP-4 | Dipeptidyl peptidase-4 |
| DRC | Dose-response curve |
| DT | Distal tubule |
| d-TC | d-Tubocurarine |
| E | Ethambutol |
| EACA | Epsilon amino caproic acid |
| e.c.f. | Extracellular fluid |
| ECG | Electrocardiogram |
| EDRF | Endothelium dependent relaxing factor |
| EDTA | Ethylene diamine tetraacetic acid |
| EEG | Electroencephalogram |
| EFV | Efavirenz |
| β-END | β-Endorphin |
| EPEC | Enteropathogenic *E. coli* |
| ERP | Effective refractory period |
| EPSP | Excitatory postsynaptic potential |
| ER | Estrogen receptor |
| ES | Extrasystole |
| ESR | Erythrocyte sedimentation rate |
| ETEC | Enterotoxigenic *E. coli* |
| Etm | Ethionamide |
| FA | Folic acid |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FFA | Free fatty acid |
| FQ | Fluoroquinolone |
| FSH | Follicle stimulating hormone |
| 5-FU | 5-Fluorouracil |
| GABA | Gamma amino butyric acid |
| GC | Guanylyl cyclase |
| GDP | Guanosine diphosphate |
| GERD | Gastroesophageal reflux disease |
| g.f.r. | Glomerular filtration rate |
| GH | Growth hormone |
| g.i.t. | Gastrointestinal tract |
| GITS | Gastrointestinal therapeutic system |
| GLP-1 | Glucagon-like peptide-1 |
| GLUT | Glucose transporter |
| GnRH | Gonadotropin releasing hormone |
| G-6-PD | Glucose-6-phosphate dehydrogenase |
| GTCS | Generalised tonic-clonic seizures |
| GTN | Glyceryl trinitrate |
| GTP | Guanosine triphosphate |
| H | Isoniazid (Isonicotinic acid hydrazide) |
| Hb | Haemoglobin |
| HBV | Hepatitis B virus |
| HCG | Human chorionic gonadotropin |
| HCV | Hepatitis C virus |
| HDL | High density lipoprotein |
| 5-HIAA | 5-Hydroxyindole acetic acid |
| HETE | Hydroxyeicosa tetraenoic acid |
| HIV | Human immunodeficiency virus |
| HMG-CoA | Hydroxymethyl glutaryl coenzyme A |
| HPA axis | Hypothalamo-pituitary-adrenal axis |
| HPETE | Hydroperoxy eicosatetraenoic acid |
| hr | Hour |
| HR | Heart rate |
| HRT | Hormone replacement therapy |
| HSV | Herpes simplex virus |
| 5-HT | 5-Hydroxytryptamine |
| 5-HTP | 5-Hydroxytryptophan |
| HVA | Homovanillic acid |
| ICSH | Interstitial cell stimulating hormone |
| IDL | Intermediate density lipoprotein |
| IGF | Insulin-like growth factor |
| IL | Interleukin |
| ILEU | Isoleucine |
| i.m. | Intramuscular |
| INH | Isonicotinic acid hydrazide |
| INR | International normalized ratio |
| i.o.t. | Intraocular tension |
| $IP_3$ | Inositol trisphosphate |
| IPSP | Inhibitory postsynaptic potential |
| IU | International unit |
| i.v. | Intravenous |
| JAK | Janus-kinase |
| KTZ | Ketoconazole |
| LA | Local anaesthetic |
| L-AMB | Liposomal amphotericin B |
| LC-3-KAT | Long chain 3-ketoacyl-CoA thiolase |
| LDL | Low density lipoprotein |
| LES | Lower esophageal sphincter |
| leu-ENK | Leucine enkephalin |
| LH | Luteinizing hormone |
| liq | Liquid |
| LMW | Low molecular weight |
| LOX | Lipoxygenase |
| LT | Leukotriene |
| MAC | Minimal alveolar concentration |
| MAC | *Mycobacterium avium* complex |
| MAO | Monoamine oxidase |
| MAPKinase | Mitogen activated protein kinase |
| max | Maximum |
| MBC | Minimum bactericidal concentration |

| | |
|---|---|
| MBL | Multibacillary leprosy |
| MDR | Multidrug resistant |
| MDT | Multidrug therapy (of leprosy) |
| met-ENK | Methionine enkephalin |
| mEq | milliequivalent |
| MFP | Monofluorophosphate (sodium) |
| MHC | Major histocompatibility complex |
| MI | Myocardial infarction |
| MIC | Minimal inhibitory concentration |
| min | Minimum |
| MIT | Monoiodo tyrosine |
| MLCK | Myosin light chain kinase |
| 6-MP | 6-Mercaptopurine |
| MRP2 | Multidrug resistance associated protein 2 |
| MRSA | Methicillin resistant *Staphylococcus aureus* |
| Mtx | Methotrexate |
| MW | Molecular weight |
| NA | Noradrenaline |
| NABQI | N-acetyl-p-benzoquinoneimine |
| NACO | National AIDS Control Organization |
| NADP | Nicotinamide adenine dinucleotide phosphate |
| NADPH | Reduced nicotinamide adenine dinucleotide phosphate |
| NAG | N-acetyl glucosamine |
| NAM | N-acetyl muramic acid |
| NANC | Nonadrenergic noncholinergic |
| NaSSA | Noradrenergic and specific serotonergic antidepressant |
| NAT | N-acetyl transferase |
| NEE | Norethindrone enanthate |
| NET | Norepinephrine transporter |
| NFAT | Nuclear factor of activated T-cell |
| NIS | $Na^+$ iodide symporter |
| NLEP | National leprosy eradication programme |
| NMDA | N-methyl-D-aspartate |
| NNRTI | Nonnucleoside reverse transcriptase inhibitor |
| NPV | Nevirapine |
| NPY | Neuropeptide-Y |
| NR | Nicotinic receptor |
| N-REM | Non-rapid eye movement (sleep) |
| NRTI | Nucleoside reverse transcriptase inhibitor |
| NSAID | Nonsteroidal antiinflammatory drug |
| NTS | Nucleus tractus solitarius |
| OATP | Organic anion transporting polypeptide |
| OC | Oral contraceptive |
| OCD | Obsessive-compulsive disorder |
| OCT | Organic cation transporter |
| OD | Once daily |
| ORS | Oral rehydration salt (solution) |
| ORT | Oral rehydration therapy |
| PABA | Paraamino benzoic acid |
| PAE | Postantibiotic effect |
| 2-PAM | Pralidoxime |
| PAS | Paraamino salicylic acid |
| PBPs | Penicillin binding proteins |
| PBL | Paucibacillary leprosy |
| PD | Parkinson's disease |
| PDE | Phosphodiesterase |
| PEP | Postexposure prophylaxis (of HIV) |
| PF | Purkinje fibre |
| PFOR | Pyruvate: ferredoxin oxidoreductase |
| PG | Prostaglandin |
| $PGI_2$ | Prostacyclin |
| P-gp | P-glycoprotein |
| PI | Protease inhibitor |
| $PIP_2$ | Phosphatidyl inositol-4, 5-bisphosphate |
| PKA | Protein kinase: cAMP dependent |
| PKC | Protein kinase C |
| $PL_A$ | Phospholipase A |
| $PL_C$ | Phospholipase C |
| PnG | Penicillin G |
| POMC | Pro-opio melanocortin |
| PP | Partial pressure |
| PPARγ | Paroxysome proliferator-activated receptor γ |
| PPH | Postpartum haemorrhage |
| PPI | Proton pump inhibitor |
| ppm | Part per million |
| PPNG | Penicillinase producing *N. gonorrhoeae* |
| PSVT | Paroxysmal supra-ventricular tachycardia |
| PT | Proximal tubule |
| PTCA | Percutaneous transluminal coronary angioplasty |
| PTH | Parathyroid hormone |
| PTP | Post-tetanic potentiation |
| PTSD | Post-traumatic stress disorder |
| QID | Four times a day |
| R | Rifampin (Rifampicin) |
| RAS | Renin-angiotensin system |
| RBP | Retinol binding protein |
| REM | Rapid eye movement (sleep) |
| RIMA | Reversible inhibitor of MAO-A |
| rINN | Recommended international nonproprietary name |
| RMP | Resting membrane potential |
| RNA | Ribonucleic acid |
| RNTCP | Revised National Tuberculosis Control Programme |
| RP | Refractory period |
| RTF | Resistance transfer factor |
| S | Streptomycin |
| SA | Sinoatrial (node) |
| SABE | Subacute bacterial endocarditis |
| s.c. | Subcutaneous |

| | |
|---|---|
| SCh | Succinylcholine |
| SERM | Selective estrogen receptor modulator |
| SERT | Serotonin transporter |
| SGA | Second generation antihistaminic |
| s.l. | Sublingual |
| SLC | Solute carrier (transporter) |
| SLE | Systemic lupus erythematosus |
| SMON | Subacute myelo-optic neuropathy |
| SNRI | Serotonin and noradrenaline reuptake inhibitor |
| s.o.s. | as required |
| SPS | Simple partial seizures |
| SR | Sustained release |
| SRS-A | Slow reacting substance of anaphylaxis |
| SSRIs | Selective serotonin reuptake inhibitors |
| STAT | Signal transducer and activator of transcription |
| susp | Suspension |
| SWS | Slow wave sleep |
| syr | Syrup |
| t½ | Half-life |
| $T_3$ | Triiodothyronine |
| $T_4$ | Thyroxine |
| tab | Tablet |
| TAL | Thick ascending limb of loop of Henle |
| TB | Tubercle bacilli |
| 3-TC | Lamivudine |
| TCAs | Tricyclic antidepressants |
| TDF | Tenofovir disoproxil fumarate |
| TDS | Three times a day |
| TG | Triglyceride |
| 6-TG | 6-Thioguanine |
| THC | Tetrahydrocannabinol |
| THFA | Tetrahydro folic acid |
| THR | Threonine |
| TIAs | Transient ischaemic attacks |
| TNF-α | Tumour necrosis factor α |
| t-PA | Tissue plasminogen activator |
| t.p.r. | Total peripheral resistance |
| TR | Thyroid hormone receptor |
| TRH | Thyrotropin releasing hormone |
| TSH | Thyroid stimulating hormone |
| TTS | Transdermal therapeutic system |
| TX | Thromboxane |
| U | Unit |
| UDP | Uridine diphosphate |
| UFH | Unfractionated heparin |
| UGT | UDP-glucuronosyl transferase |
| UT | Urea transporter |
| V | Volume of distribution |
| VAL | Valine |
| VF | Ventricular fibrillation |
| Vit | Vitamin |
| VLDL | Very low density lipoprotein |
| VMA | Vanillyl mandelic acid |
| VRE | Vancomycin resistant enterococci |
| VRSA | Vancomycin resistant *Staphylococcus aureus* |
| VT | Ventricular tachycardia |
| WPW | Wolff-Parkinson-White syndrome |
| Z | Pyrazinamide |
| ZE syndrome | Zollinger-Ellison syndrome |

# Section 1

# General Pharmacological Principles

## Section Outline

1. Introduction, Routes of Drug Administration
2. Pharmacokinetics
3. Pharmacodynamics
4. Adverse Drug Effects

CHAPTER 1

# Introduction, Routes of Drug Administration

## INTRODUCTION

### Pharmacology

Pharmacology is the science of drugs (Greek: Pharmacon—drug; logos—discourse in). In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living systems, and any chemical substance which can produce a biological response is a 'drug.' Pharmacology encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use of drugs for medicinal purposes.

In the context of dental practice, a broad understanding of pharmacology with emphasis on certain aspects is imperative because:

- Dentists have to prescribe/use drugs, albeit from a limited range, for the treatment of dental conditions.
- Many dental patients concurrently suffer from other medical conditions, e.g. diabetes, hypertension, arthritis, etc. for which they may be taking drugs that may have dental implications or may interact with drugs prescribed by the dentist.
- The dentist may have to deal with a medical emergency arising in the dental office during the course of a procedure.

For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Only the overt effects of these substances on the body were known, that too rather imprecisely; but how the same were produced was entirely unknown. Over the past 150 years or so, drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs have been developed. The mechanism of action including molecular target of many drugs has been elucidated. This has been possible due to prolific growth of pharmacology which forms the backbone of rational therapeutics.

The two main divisions of pharmacology are *pharmacodynamics* and *pharmacokinetics*.

**Pharmacodynamics** (Greek: *dynamis*—power)—What the drug does to the body.

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels, e.g. adrenaline → interaction with adrenoceptors → G-protein mediated stimulation of cell membrane bound adenylyl cyclase → increased intracellular cyclic 3′,5′AMP → cardiac stimulation, hepatic glycogenolysis and hyperglycaemia, etc.

**Pharmacokinetics** (Greek: *Kinesis*—movement)—What the body does to the drug.

This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug, e.g. paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at 30–60 min; 25% bound to plasma proteins, widely and almost uniformly distributed in the body (volume of distribution ~ 1 L/kg); extensively metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites which are excreted in urine; has a plasma half-life (t½) of 2–3 hours and a clearance value of 5 ml/kg/min.

**Drug** (French: *Drogue*—a dry herb) *It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease.*

The WHO (1966) has given a more comprehensive definition—*"Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."*

The term 'drugs' is being also used to mean addictive/abused substances. However, this restricted and derogatory sense usage is unfortunate degradation of a time honoured term, and 'drug' should refer to a substance that has some therapeutic/health promoting/diagnostic application.

Some other important aspects of pharmacology are:

**Pharmacotherapeutics** It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment in accordance with the stage of disease and the specific features of a patient are a part of pharmacotherapeutics.

**Clinical pharmacology** It is the scientific study of drugs (both new and old) in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers as well as in patients; evaluation of efficacy and safety of drugs and comparative trials with other forms of treatment; surveillance of patterns of drug use, adverse effects, etc.

The aim of clinical pharmacology is to generate data for optimum use of drugs and for practice of medicine to be 'evidence based'.

**Chemotherapy** It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with no/minimal effects on the host cells.

Drugs, in general, can thus be divided into:

*Pharmacodynamic agents* These are designed to have pharmacodynamic effects in the recipient.

*Chemotherapeutic agents* These are designed to inhibit/kill invading parasites/malignant cell, but have no/minimal pharmacodynamic effects in the recipient.

**Pharmacy** It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called *Pharmaceutics*, which is primarily a technological science.

**Toxicology** It is the study of poisonous effect of drugs and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

## Sources of drugs

Drugs are obtained from a variety of sources:

1. *Plants* Many plants contain biologically active substances and are the oldest source of drugs. Chemically, the active ingredients of plants fall in several categories:
   a. *Alkaloids:* These are alkaline nitrogenous bases having potent activity, and are the most important category of vegetable origin drugs. Prominent examples are: morphine, atropine, ephedrine, nicotine, ergotamine, reserpine, quinine, vincristine, etc. They are mostly used as their water soluble hydrochloride/sulfate salts.
   b. *Glycosides:* These compounds consist of a heterocyclic nonsugar moiety (aglycone) linked to a sugar moiety through ether linkage. Cardiac glycosides (digoxin, ouabain) are the best known glycosidic drugs. The active principle of senna and similar plant purgatives are anthraquinone glycosides. Aminoglycosides (gentamicin, etc.) are antibiotics obtained from microorganisms, and have an aminosugar in place of a sugar moiety.
   c. *Oils:* These are viscous, inflammable liquids, insoluble in water. *Fixed* (nonvolatile) oils are calorie yielding triglycerides of higher fatty acids; mostly used for food and as emollients, e.g. groundnut oil, coconut oil, sesame oil, etc. Castor oil is a stimulant purgative. *Essential* (volatile) oils, mostly obtained from flowers or leaves are aromatic (fragrant) terpene hydrocarbons that have no food value. They are used as flavouring agents, carminatives, counterirritants and astringents; examples are eucalyptus oil, pepermint oil, nilgiri oil, etc. Clove oil is used to allay dental pain. Menthol, thymol, camphor are volatile oils that are solids at room temperature and are included in mouth washes, tooth pastes.
   *Mineral oils* are not plant products, but obtained from petroleum; liquid paraffin is a lubricant laxative, soft and hard paraffin are used as emollient and as ointment bases.

Other plant products like tanins are astringent; gums are demulcents and act as suspending agents in liquid dosage forms. Glycerine is a viscous, sweet liquid used as vehicle for gum/throat paint. Resins and balsams are used as antiseptic and in cough mixtures. The antimalarial drug artemisinin is a sesquiterpene endoperoxide obtained from a Chinese plant.

2. *Animals* Though animal parts have been used as cures since early times, it was exploration of activity of organ extracts in the late 19th and early 20th century that led to introduction of animal products into medicine, e.g. adrenaline, thyroxine, insulin, liver extract (vit. $B_{12}$). Antisera and few vaccines are also produced from animals.
3. *Microbes* Most antibiotics are obtained from fungi, actinomycetes and bacteria, e.g. penicillin, gentamicin, tetracycline, erythromycin, polymyxin B, actinomycin D (anticancer). Some enzymes, e.g. diastase from a fungus and streptokinase from streptococci have a microbial source. Vaccines are produced by the use of microbes.
4. *Minerals* Few minerals, e.g. iron salts, calcium salts, lithium carbonate, magnesium/aluminium hydroxide, iodine are used as medicinal substances.
5. *Synthetic chemistry* Synthetic chemistry made its debut in the 19th century, and is now the largest source of medicines. Not only diverse congeners

of naturally obtained drugs (atropine substitutes, adrenergic $\beta_2$ agonists, synthetic glucocorticoids/progestins/cephalosporins, etc.) have been introduced to achieve greater selectivity of action or even novel type of activity, but many entirely synthetic families of drugs, e.g. benzodiazepines, thiazides, benzimidazoles, fluoroquinolones, etc. have been produced. Many drugs are being synthesized to target specific biomolecules, e.g. ACE inhibitors, glycoprotein IIb/IIIa receptor antagonists, HIV-reverse transcriptase inhibitors, etc. Synthetic drugs that are *chiral* can be produced as single active enantiomer products, which may be therapeutically superior.

6. *Biotechnology* Several drugs, especially peptides and proteins are now produced by recombinant DNA technology, e.g. human growth hormone, human insulin, altaplase, interferon, etc. Monoclonal antibodies, regulator peptides, erythropoietin and other growth factors are the newer drugs of biotechnological origin.

## Drug nomenclature

A drug generally has three categories of names:

*(a) Chemical name* It describes the substance chemically, e.g. 1-(Isopropylamino)-3-(1-naphthyloxy) propan-2-o1 for propranolol. This is cumbersome and not suitable for use in prescribing. A code name, e.g. RO 15-1788 (later named flumazenil) may be assigned by the manufacturer for convenience and simplicity before an approved name is coined.

*(b) Nonproprietary name* It is the name accepted by a competent scientific body/authority, e.g. the United States Adopted Name (USAN) or the British Approved Name (BAN). The nonproprietary names of newer drugs are kept uniform by an agreement to use the 'recommended International Nonproprietary Name (rINN)' only. However, many older drugs have more than one nonproprietary names, e.g. meperidine (USA) and pethidine (UK, India) for the same drug. Until the drug is included in a pharmacopoeia, the nonproprietary name may also be called the approved name. After its appearance in the official publication, it becomes the *official name*.

In common parlance, the term generic name is used in place of nonproprietary name. Etymologically this is incorrect: 'generic' should be applied to the chemical or pharmacological group (or genus) of the compound, e.g. aminoglycoside antibiotics, tricyclic antidepressants, etc.; but has become synonymous with nonproprietary name. A legitimate '*generic medicine*' should be chemically, pharmacokinetically and therapeutically equivalent to the reference 'branded medicine'.

*(c) Proprietary (Brand) name* It is the name assigned by the manufacturer(s) and is his property or trade mark. One drug may have multiple proprietary names, e.g. NOVAMOX, AMOXYLIN, SYNAMOX, AMOXIL, MOX for amoxicillin from different manufacturers. Brand names are designed to be catchy, short, easy to remember and often suggestive, e.g. LOPRESOR suggesting drug for lowering blood pressure. Brand names generally differ in different countries, e.g. timolol maleate eyedrops are marketed as TIMOPTIC in the USA but as GLUCOMOL in India. Even the same manufacturer may market the same drug under different brand names in different countries. In addition, combined formulations have their own multiple brand names. This is responsible for much confusion in drug nomenclature.

There are many arguments for using the nonproprietary name in prescribing:

uniformity, convenience, economy and better comprehension (propranolol, sotalol, timolol, pindolol, metoprolol, acebutolol, atenolol are all β blockers, but their brand names have no such similarity). Drugs marketed under nonproprietary name (called 'generic' products) are much cheaper than their 'branded' counterparts. However, when it is important to ensure consistency of the product in terms of quality and bioavailability, etc. and especially when official control over quality of manufactured products is not rigorous, it is better to prescribe by the dependable brand name.

## Dosage forms of drugs

Dosage form is a product suitable for administration of a drug to a patient. Every active ingredient (drug) has to be formulated by adding other substances (excipients, diluents, preservatives, vehicles, etc.) according to a specific recipe and packaged into a specific 'dosage form' such as tablet, elixir, ointment, injection vial, etc. which is then administered to the subject. The dosage form provides body to the drug, demarcates single doses, protects the active ingredient(s), and makes it suitable for administration in various ways. The important dosage forms are briefly described below.

### Solid dosage forms

1. *Powders* The drug is in a dry and finely pulverised state. If the drug is for oral administration, each dose has to be wrapped separately or packed in sachets; therefore this dosage form is inconvenient and unpopular except when the quantity is several grams, e.g. oral rehydration salts. Powders for topical application (tooth powders, dusting powders) are supplied as *bulk powders* in plastic or metallic containers with holes for sprinkling. *Effervescent powders* contain granulated sod. bicarbonate and citric or tartaric acid. They react when dissolved in water to liberate $CO_2$ causing bubbling.
2. *Tablets* The drug is powdered or granulated, mixed with binding agents, and other excipients, and compressed/moulded into discoid, oblong or other shapes suitable for swallowing. The tablet may be plain or sugar coated/film coated/enteric coated, etc. *Sustained release tablets* contain drug particles which are coated to dissolve at different rates. In *controlled release tablets* a semipermeable membrane controls release of the drug. Other specialized *gastrointestinal therapeutic systems* have also been developed.
3. *Pills* These are archaic dosage forms in which the drug powder is mixed with honey/syrup to make a sticky mass. This is then rolled into spherical/oval bodies meant to be swallowed. The term is often loosely applied to tablets as well.
4. *Capsules* These are water soluble cylindrical containers made of gelatin which are filled with powdered or liquid medicament. The container dissolves on swallowing so that the drug is released in the stomach. *Enteric coated* capsules are designed to dissolve only on reaching the ileum. *Spansules* are extended release capsules which are packed with granules of the drug having different coatings to dissolve over a range of time periods.
5. *Lozenges* These are tablet-like bodies of various shapes containing the drug along with a suitable gum, sweetening and flavouring agents. They are to be retained in the mouth and allowed to dissolve slowly providing the drug for local action in the mouth and throat.
6. *Suppositories* These are conical bullet-shaped dosage forms for insertion into the anal canal, in which the drug is mixed with a mouldable firm base that melts

at body temperature and releases the contained drug. Oval or suitably shaped bodies for vaginal insertion are called '*pessaries*', while elongated pencil-like cones meant for insertion into male or female urethra are called *bougies*.

### Liquid dosage forms

1. *Aqueous solutions* They contain the drug dissolved in water, which may be meant for oral, topical or parenteral administration. Oral drug solutions often contain sweetening and flavouring agents. Preservatives have to be mostly added because shelf-life of watery solutions is short.
2. *Suspensions* are dispersion of insoluble drugs in water with the help of a suspending agent. *Emulsions* are uniform mixtures of two immiscible liquids (mostly oil and water) in which droplets of one (dispersed phase) are suspended in the other (continuous phase) with the help of an amphiphilic emulsifying agent. Milk is a naturally occurring emulsion. Both suspensions and emulsions tend to settle down on keeping; should be shaken thoroughly before use.
3. *Elixirs* are hydro-alcoholic solutions of drugs, usually sweetened with syrup and flavoured by fruit extracts. *Syrups* have higher concentration of sugar and are thicker in consistency. Drugs that deteriorate in aqueous medium are dispensed in bottles as *dry syrups* which are reconstituted by adding measured quantity of water and shaking. The reconstituted suspension must be used within a few days. *Linctus* is a viscous syrupy liquid meant to be licked slowly for soothing the throat. It generally has menthol to impart cooling sensation, and an antitussive.
4. *Drops* These are relatively more concentrated solutions of medicaments meant for oral ingestion or external application to eye, nose or ear canal. Oral drops are the preferred dosage form for infants and young children. Eye/nasal drops should be isotonic. Eye drops need sterilization. Drops are supplied in vials with a nozzle, or alongwith a dropper for accurate dosing.
5. *Lotions* These are solutions, suspensions or emulsions meant for external application to the skin without rubbing. They generally have soothing, cooling, protective or emollient property. *Liniments* are similar preparations which generally contain counterirritants, and are to be rubbed on the skin to relieve pain and cause rubefaction.
6. *Injections* These are sterile solutions or suspensions in aqueous or oily medium for subcutaneous or intramuscular administration. Only aqueous solutions (not suspensions) are suitable for intravenous (i.v.) injection, because particles in suspension and oils injected i.v. can cause embolism. Injections are supplied in sealed glass *ampoules* or air tight rubber capped *vials*. Ampoules are broken just before injection, and usually contain a single dose. Drug from the vial is sucked in a syringe by piercing the rubber cap. Vials may be single-dose or multi-dose. Drugs which are unstable in solution are supplied as dry powder vials. Sterile solvent is injected in the vial and the dissolved/suspended drug is then sucked out into the syringe just before administration. Large volume i.v. infusions are marketed in glass/polypropylene bottles.

### Semisolid dosage forms

1. *Ointments* These are greasy semisolid preparations meant for external application to the skin, eye, nasal mucosa, ear or anal canal. The drug is

incorporated in an oily base, such as soft or hard paraffin, wool fat, bee's wax, etc. Ointments are not suitable for oozing surfaces, because they do not allow evaporation of water. *Creams* are similar to ointment but the base is a water in oil emulsion.

2. *Pastes* These are nongreasy preparations of thick consistency containing hydrophilic adhesive powders such as starch, prepared chalk, aluminium/magnesium hydroxide, zinc oxide, carboxy methylcellulose, etc. which swell by absorbing water. Pastes may contain viscous nonoily liquids like glycerol or propylene glycol. Pastes can be applied to inflamed or excoriated skin, oozing surfaces, teeth and mucous membranes. Toothpastes are items of personal hygiene, and medicated toothpastes are extensively used in dentistry.
3. *Gels* The medicament is incorporated in a viscous colloidal solution of gelatin or similar material and is usually dispensed in collapsible tubes. They are meant for external application to the skin or mucosa and provide longer duration contact, but are nongreasy and washable with water. Gels are commonly applied to oral ulcers because they are better retained than aqueous solutions. Many toothpastes are gels.

### Inhalations

Drugs which are gases or volatile liquids can be administered by inhalation carried into air or oxygen with the help of a mouth piece, face mask, hood or endotracheal tube. Nonvolatile liquids and fine particle solids can be aerosolized using a metered dose inhaler, jet nebulizer, rotahaler or spinhaler for inhalation through the mouth. *Pressurized metered dose inhalers* (PMDIs) are hand-held devices which use a propellant, mostly hydrofluoroalkane (HFA), and deliver a specified dose of the drug in aerosol form per actuation. *Jet nebulizers* produce a mist of the drug solution generated by pressurized air or oxygen. *Rotahaler* is also a portable device in which a capsule (rotacap) containing very fine powder of the drug is punctured during actuation and the released particles are aerosolized by the inspiratory airflow of the patient. A propellant can also be used in some *spin halers.* Efficacy of the aerosolized drug depends on the particle size: 1–5 μm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while <1 μm particles do not settle anywhere and are exhaled out.

### Prescription and non-prescription drugs

As per drug rules, majority of drugs including all antibiotics must be sold in retail only against a prescription issued to a patient by a registered medical practitioner. These are called 'prescription drugs'. In India such drugs have been placed in the *schedule H* of the Drugs and Cosmetic Rules (1945) as amended from time to time. However, few drugs like simple analgesics (paracetamol, aspirin), antacids, laxatives (senna, lactulose), vitamins, ferrous salts, etc. are considered relatively harmless, and can be procured without a prescription. These are 'non-prescription' or 'over-the-counter' (OTC) drugs; can be sold even by grocery stores.

## ROUTES OF DRUG ADMINISTRATION

Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drug as well as patient-related factors. Mostly common sense considerations, feasibility and convenience dictate the route to be used.

**Factors governing choice of route**

1. Physical and chemical properties of the drug (solid/liquid/gas; solubility, stability, pH, irritancy).
2. Site of desired action—localized and approachable or generalized and not approachable.
3. Rate and extent of absorption of the drug from different routes.
4. Effect of digestive juices and first pass metabolism on the drug.
5. Rapidity with which the response is desired (routine treatment or emergency).
6. Accuracy of dosage required (i.v. and inhalational can provide fine tuning).
7. Condition of the patient (unconscious, vomiting).

Routes can be broadly divided into those for (a) local action and (b) systemic action.

### LOCAL ROUTES

These routes can only be used for localized lesions at accessible sites and for drugs whose systemic absorption from these sites is minimal, slow or absent. Thus, high concentrations are attained at the desired site without exposing the rest of the body. Systemic side effects or toxicity are consequently absent or minimal. For drugs (in suitable dosage forms) that are absorbed from these sites/routes, the same can serve as a systemic route of administration. The local routes are:

**1. Topical** This refers to external application of the drug to the surface for localized action. It is often more convenient and efficient mode of delivering the drug to skin, oropharyngeal/nasal mucosa, eyes, ear canal, anal canal, vagina, etc. Nonabsorbable drugs given orally for action on g.i. mucosa (sucralfate, neomycin), inhalation of drugs for action on bronchi (salbutamol, fluticasone propionate) and irrigating solutions/jellies (povidone iodine, lidocaine) applied to urethra are other forms of topical medication. In dental practice antiseptics, astringents, haemostatics are often applied as paints, toothpastes, mouthwashes, gargles or lozenges.

**2. Deeper tissues** Certain deep areas can be approached by using a syringe and needle, but the drug should be in such a form that systemic absorption is slow, e.g. infiltration around a nerve or intrathecal injection (lidocaine, amphotericin B), intra-articular injection (hydrocortisone acetate), retrobulbar injection (hydrocortisone acetate).

**3. Arterial supply** Close intra-arterial injection is used for contrast media in angiography; anticancer drugs can be infused in femoral or brachial artery to localize the effect for limb malignancies.

### SYSTEMIC ROUTES

The drug administered through systemic routes is intended to be absorbed into bloodstream and distributed all over, including the site of action, through circulation (Fig. 1.1).

**1. Oral**

Oral ingestion is the oldest and commonest mode of drug administration. It is safer, more convenient, does not need assistance, noninvasive, often painless, the medicament need not be sterile and so is cheaper. Both solid dosage forms (powders, tablets,

capsules, spansules, dragees, moulded tablets, gastrointestinal therapeutic systems—GITs) and liquid dosage forms (elixirs, syrups, emulsions, mixtures) can be given orally.

**Limitations of oral route of administration**

- Action is slower and thus not suitable for emergencies.
- Unpalatable drugs (chloramphenicol) are difficult to administer; drug may be filled in capsules to circumvent this.
- May cause nausea and vomiting.
- Cannot be used for uncooperative/unconscious/vomiting patient.
- Certain drugs (e.g. gentamicin) are not absorbed. Absorption of some drugs is variable and not dependable.
- Some drugs are destroyed by digestive juices (penicillin G, insulin) or in liver (glyceryl trinitrate, testosterone, lidocaine) by high first pass metabolism.

### 2. Sublingual (s.l.) or buccal

The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa. Only lipid-soluble and non-irritating drugs can be so administered. Absorption is relatively rapid—action can be produced in minutes. Though it is somewhat inconvenient, one can spit the remaining drug after the desired effect has been obtained. The chief advantage is that liver is bypassed and drugs with high first pass metabolism can be absorbed directly into systemic circulation. Drugs given sublingually are—glyceryl trinitrate, buprenorphine, desamino-oxytocin.

### 3. Rectal

Certain drugs put into rectum as suppositories or retention enema get absorbed and produce systemic effect. This route is particularly utilized for irritant or unpleasant drugs, as well as for a patient having recurrent vomiting. However, rectal route is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable, though diazepam solution and paracetamol suppository are dependably absorbed from the rectum in children. Drug absorbed into external haemorrhoidal veins (about 50%) bypasses liver, but not that absorbed into internal haemorrhoidal veins. Rectal inflammation can result from irritant drugs. Indomethacin, diazepam, ergotamine and a few other drugs are sometimes given rectally.

### 4. Cutaneous

Highly lipid-soluble drugs can be applied over the skin for slow and prolonged absorption. The liver is also bypassed. The drug can be incorporated in an ointment and applied over specified area of skin.

Transdermal therapeutic systems (TTS) These are devices in the form of adhesive patches of various shapes and sizes (5–20 $cm^2$) which deliver the contained drug at a constant rate into the systemic circulation via the stratum corneum (Fig. 1.2). The drug (in solution or bound to a polymer) is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the undersurface of which is smeared with an adhesive impregnated with priming dose of the drug that is protected by another film to be peeled off just before application. The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. The micropore membrane is such that rate of drug delivery to the skin surface is less than the slowest rate of absorption from skin. This offsets any variation in the rate of absorption according to the properties of different sites. As such, drug is delivered at constant and predictable rate irrespective of site of application, which is usually chest, abdomen, upper arm, lower back, buttock or mastoid region.

Transdermal patches of glyceryl trinitrate, fentanyl, nicotine and estradiol are available in India, while those of isosorbide dinitrate, hyoscine, and clonidine are marketed elsewhere. For different drugs, transdermal patches have been designed to last 1–3 days. They are relatively more expensive than oral dosage forms, but first pass metabolism is avoided. Local irritation and erythema occurs in some, but is generally mild; can be minimized by changing the site of application each time by rotation. Discontinuation has been necessary in 2 to 7% cases.

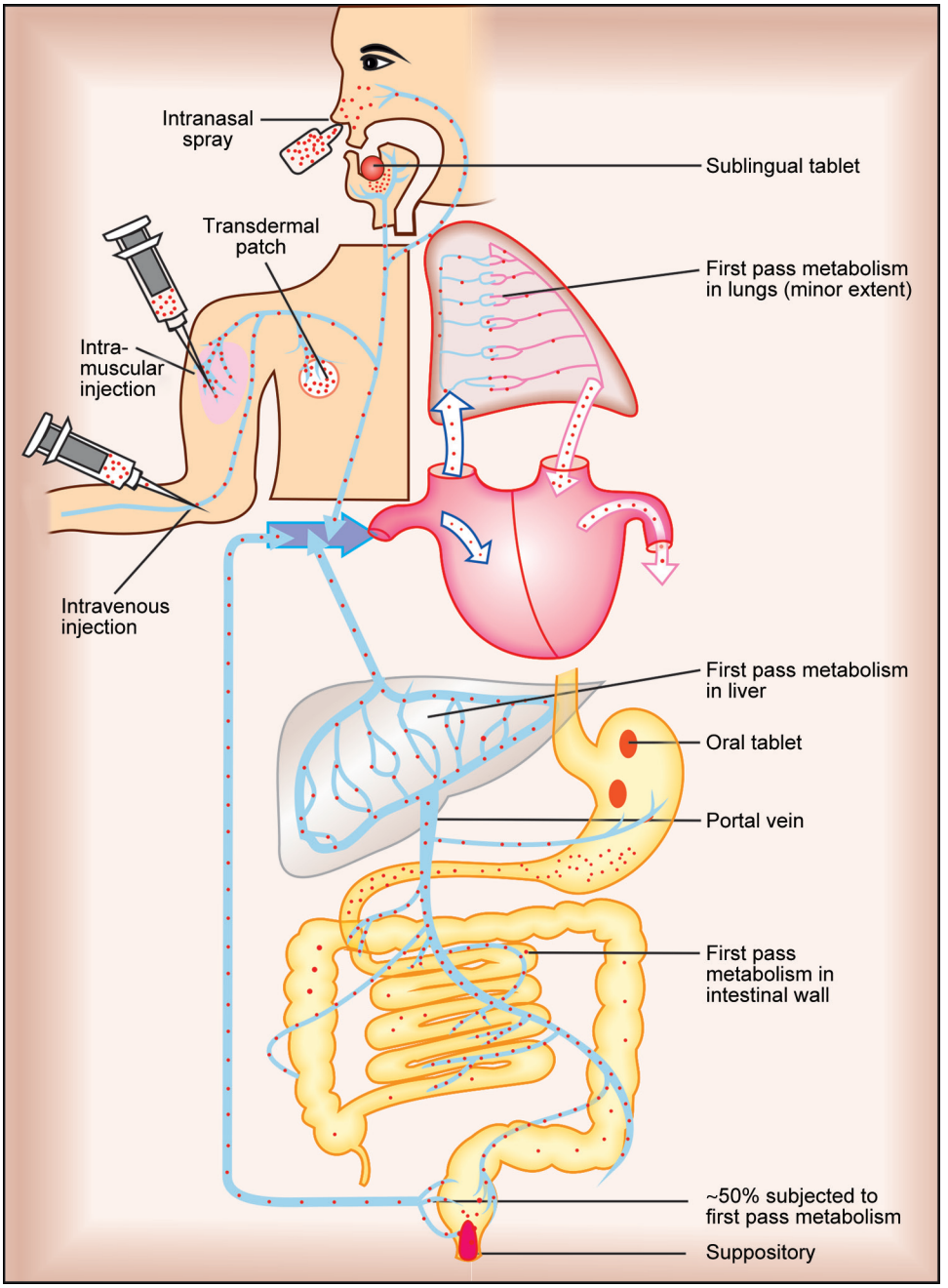


**Fig. 1.1:** Vascular pathway of drugs absorbed from various systemic routes of administration, and sites of first pass metabolism

*Note:* All the drug administered orally is subjected to first pass metabolism in intestinal wall and liver, while approximately half of that absorbed from rectum passes through liver. Drug entering from any systemic route is exposed to first pass metabolism in lungs, but its extent is minor for most drugs.

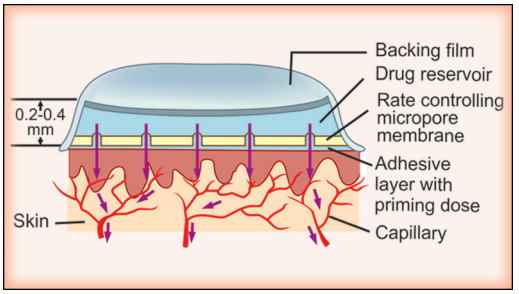


**Fig. 1.2:** Illustration of a transdermal drug delivery system

### 5. Inhalation

Volatile liquids and gases are given by inhalation for systemic action, e.g. general anaesthetics. Absorption takes place from the vast surface of alveoli—action is very rapid. When administration is discontinued, the drug diffuses back and is rapidly eliminated in expired air. Thus, controlled administration is possible with moment-to-moment adjustment. Irritant vapours (ether) cause inflammation of respiratory tract and increase secretion.

### 6. Nasal

The mucous membrane of the nose can readily absorb many drugs. Digestive juices and liver are bypassed. However, only certain drugs like GnRH agonists and desmopressin applied as a spray or nebulized solution have been used by this route.

### 7. Parenteral

(*Par*—beyond, enteral—intestinal)
Conventionally, 'parenteral' refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the enteral mucosa. The limitations of oral administration are circumvented. Drug action is faster and surer (this is valuable in emergencies). Gastric irritation and vomiting are not provoked. Parenteral route can be employed even in unconscious, uncooperative or vomiting patient. There are no chances of interference by food or digestive juices. Liver is bypassed.

Disadvantages of parenteral routes are—the preparation has to be sterilized and is costlier, the technique is invasive and painful, assistance of another person is mostly needed (though self-injection is possible, e.g. insulin by diabetics), there are chances of local tissue injury, and in general it is more risky than oral. The important parenteral routes are:

**(i) Subcutaneous (s.c.)** The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (irritant drugs cannot be injected) but is less vascular (absorption is slower). Self-injection is possible because deep penetration is not needed. This route should be avoided in shock patients who are vasoconstricted—absorption will be delayed. Repository (depot) preparations—oily solutions or aqueous suspensions can be injected for prolonged action.

Some special forms of this route are:

(a) *Dermojet* In this method needle is not used; a high velocity jet of drug solution is projected from a microfine orifice using a gun-like implement. The solution passes through the superficial layers and gets deposited in the subcutaneous tissue. It is essentially painless and suited for mass inoculations.

(b) *Pellet implantation* The drug as solid pellet is introduced with a trochar and cannula. This provides sustained release of the drug over weeks and months, e.g. DOCA, testosterone.

(c) *Sialistic (nonbiodegradable) and biodegradable implants* Crystalline drug is packed in tubes/capsules made of suitable materials and implanted under the skin. Slow and uniform leaching of the drug occurs over months providing constant blood levels. The nonbiodegradable implant has to be removed later on but not the biodegradable one. This has been tried for hormones and contraceptives (e.g. NORPLANT).

**(ii) Intramuscular (i.m.)** The drug is injected in one of the large skeletal muscles—deltoid, triceps, gluteus maximus, rectus femoris, etc. Muscle is less richly supplied with sensory nerves (mild irritants can be injected) and

is more vascular (absorption is faster). It is less painful, but self-injection is often impracticable—deep penetration is needed. Depot preparations can be injected by this route. Intramuscular injection should be avoided in patients taking anticoagulant medication.

**(iii) Intravenous (i.v.)** The drug is injected as a bolus (Greek: bolos-lump) or infused slowly over hours in one of the superficial veins. The drug reaches directly into the bloodstream and effects are produced immediately. This is of great value in emergency. The intima of veins is insensitive and drug gets diluted with blood, therefore, even highly irritant drugs can be injected i.v., but the hazards of this route are—thrombophlebitis of the injected vein and necrosis of adjoining tissues if extravasation occurs. These complications can be minimized by diluting the drug or injecting it into a running i.v. line. Only aqueous solutions (not suspensions) can be injected i.v. and there are no depot preparations for this route. The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused. One big advantage with this route is—in case response is accurately measurable (e.g. BP) and the drug short acting (e.g. sodium nitroprusside), titration of the dose with the response is possible. However, this is the most risky route—vital organs like heart, brain, etc. get exposed to high concentrations of the drug. Possibility of causing air embolism is another risk.

**(iv) Intradermal injection** The drug is injected into the skin raising a bleb (e.g. BCG vaccine, sensitivity testing) or scarring/multiple puncture of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.

CHAPTER 2

# Pharmacokinetics

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. The overall scheme of pharmacokinetic processes is depicted in Fig. 2.1. Intensity of response is related to concentration of the drug at the site of action, which in turn is dependent on its pharmacokinetic properties. Pharmacokinetic considerations, therefore, determine the route(s) of administration, dose, latency of onset, time of peak action, duration of action and thus frequency of administration of a drug.

All pharmacokinetic processes involve transport of the drug across biological membranes.

**Biological membrane** This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix, along with adsorbed extrinsic and intrinsic protein molecules (Fig. 2.2). The proteins are able to freely float through the membrane: associate and organize or vice versa. Some of the intrinsic ones, which extend through the full thickness of the membrane, surround fine aqueous pores. Paracellular spaces or channels also exist between certain epithelial/endothelial cells. Other adsorbed proteins have enzymatic,

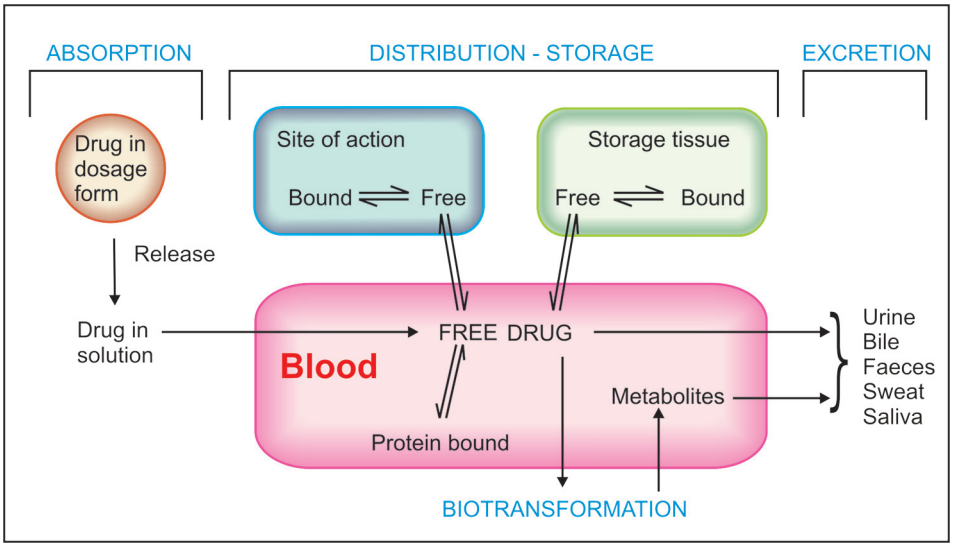


**Fig. 2.1:** Schematic depiction of pharmacokinetic processes

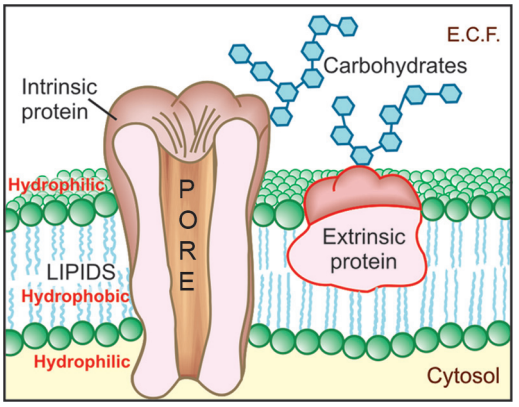


**Fig. 2.2:** Illustration of the organization of biological membrane

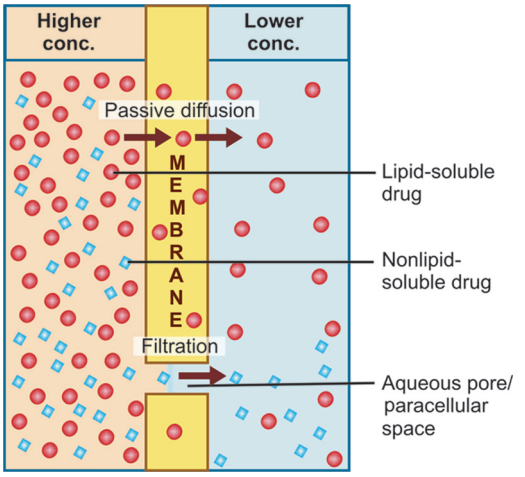


**Fig. 2.3:** Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

carrier, receptor or signal transduction properties. Lateral movement of lipid molecules also occurs. As such, biological membranes are highly dynamic structures. Drugs are transported across the membranes by:

(a) Passive diffusion and filtration.

(b) Specialized transport.

### Passive diffusion

The drug diffuses across the membrane in the direction of its concentration gradient (high to low), the membrane playing no active role in the process. This is the most important mechanism for majority of drugs, because drugs are foreign substances and specialized mechanisms are developed by the body for normal metabolites only.

Lipid-soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane (Fig. 2.3), the rate of transport being proportional to the lipid : water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Further, greater the difference in the concentration of the drug on two sides of the membrane, faster is its diffusion.

**Influence of pH** Most drugs are weak electrolytes, i.e. their ionization is pH dependent (contrast strong electrolytes which are nearly completely ionized at acidic as well as alkaline pH). The ionization of a weak acid HA is given by the equation:

$$pH = pKa + \log \frac{[A^-]}{[HA]} \quad ...(1)$$

pKa is the negative logarithm of acidic dissociation constant of the weak electrolyte. If the concentration of ionized drug $[A^-]$ is equal to the concentration of unionized drug [HA], then—

$$\frac{[A^-]}{[HA]} = 1$$

since log 1 is 0, under this condition

$$pH = pKa \quad ...(2)$$

Thus, *p*Ka is numerically equal to the pH at which the drug is 50% ionized.

If pH is increased by 1, then—

$\log [A^-]/[HA] = 1$ or $[A^-]/[HA] = 10$

Similarly, if pH is reduced by 1, then—

$[A^-]/[HA] = 1/10$

Thus, weakly acidic drugs, which form salts with cations, e.g. sod. phenobarbitone, sod. sulfadiazine, pot. penicillin-V, etc. ionize