3rd Edition

Essentials of Pharmacology *for Dentistry*

KD Tripathi

JAYPEE

Essentials of Pharmacology for Dentistry

Essentials of Pharmacology for Dentistry

3rd Edition

KD Tripathi MD
Ex-Director-Professor and Head of Pharmacology
Maulana Azad Medical College and associated
LN and GB Pant Hospitals
New Delhi, India

The Health Sciences Publisher
New Delhi | London | Philadelphia | Panama

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Offices

J.P. Medical Ltd
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-2031708910
Fax: +44(0)20 3008 6180
Email: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc
City of Knowledge, Bld. 235, 2nd Floor, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
Email: cservice@jphmedical.com

Jaypee Medical Inc
325 Chestnut Street
Suite 412, Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
Email: support@jpmedus.com

Jaypee Brothers Medical Publishers (P) Ltd
17/1-B Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
Email: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
Bhotahity, Kathmandu
Nepal
Phone: +977-9741283608
Email: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Managing Editor: M Tripathi

Essentials of Pharmacology for Dentistry

First Edition: 2005
Second Edition: 2011
Third Edition: **2016**

ISBN 978-93-85999-84-0

Printed at

Preface to the Third Edition

Relevance of *Pharmacology*, the science of drugs (medicines), 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/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 in their clinic. As such, a broad knowledge of pharmacology 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. Each chapter is organised systematically. The opening sentence defines the class of drugs, followed by their classification presented in chart form for better pictorial impression and easy remembrance. The 'prototype' approach is followed by describing the representative drug of the class. Matters particularly relevant to dental therapeutics have been highlighted by italicizing. 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, oral complications of cancer chemotherapy, conscious sedation in dentistry, etc.

The third section covers antimicrobials and other drugs which the dentists 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, 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, 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 a new 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 oro-dental conditions.

I am thankful to my colleagues in pharmacology and dentistry as well as to readers of the earlier editions for their comments and suggestions which helped in preparing the 3rd 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 and illustrations by Ms Geeta Srivastava, Mr Rakesh Kumar and the staff of M/s Jaypee Brothers Medical Publishers is highly appreciated. The participation and cooperation of my wife is sincerely acknowledged.

April 2016 **KD Tripathi**

Contents

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
ARV	Antiretrovirus
5-ASA	5-Amino salicyclic acid
Asc LH	Ascending limb of Loop of Henle
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
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
5-FC	5-Flucytosine
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)
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
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
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
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
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
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
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
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
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
TB	Tubercle bacilli
TCAs	Tricyclic antidepressants
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.p.r.	Total peripheral resistance
t-PA	Tissue plasminogen activator
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

General Pharmacological Principles

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. In other words, any chemical substance which can produce a biological response is a 'drug.' It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use 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/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 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 and 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 parasite/malignant cell and 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. It 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 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. 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 chemicals* **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 β_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.

6. *Biotechnological products* *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 due to wide usage and official acceptance.

(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.* ALTOL, ATCARDIL, ATECOR, ATEN, BETACARD, LONOL, TENOLOL, TENORMIN *for atenolol 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 b blockers, but their brand names have no such similarity). 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, demarkates 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 are supplied as** *bulk powders. 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 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 anal canal, in which the drug is mixed with a mouldable firm base that melts at body temperature. Oval or suitably shaped bodies for vaginal insertion are called** *'pessaries'*, **while elongated pencil-like ones meant for insertion into male or female urethra are called** *bougies*.

Liquid dosage forms

1. *Aqueous solutions* **They contain the drug dissolved in water; 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.
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. *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 must also be sterilized. Drops are supplied in vials with a nozzle or alongwith a dropper.
5. *Lotions* These are solutions, suspensions or emulsions meant for external application to the skin without rubbing. They generally have soothing, 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, while 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 or multi-dose. Drugs which are unstable in solution are supplied as dry powder vials. Sterile solvent is injected in the vial just before it is to be injected and the dissolved/suspended drug is then sucked out into the syringe. 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 donot 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 unbroken skin, oozing surfaces and mucous membranes. Toothpastes are items of personal hygine, 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.

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 donot 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', and in India they 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/jellys (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), intraarticular 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 (see 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 (emetine).*
- *Cannot be used for uncooperative/unconscious/vomiting patient.*
- *Certain drugs are not absorbed (streptomycin). Absorption of some drugs is erratic.*
- *Others 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 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 irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect. This route can also be used when the patient is having

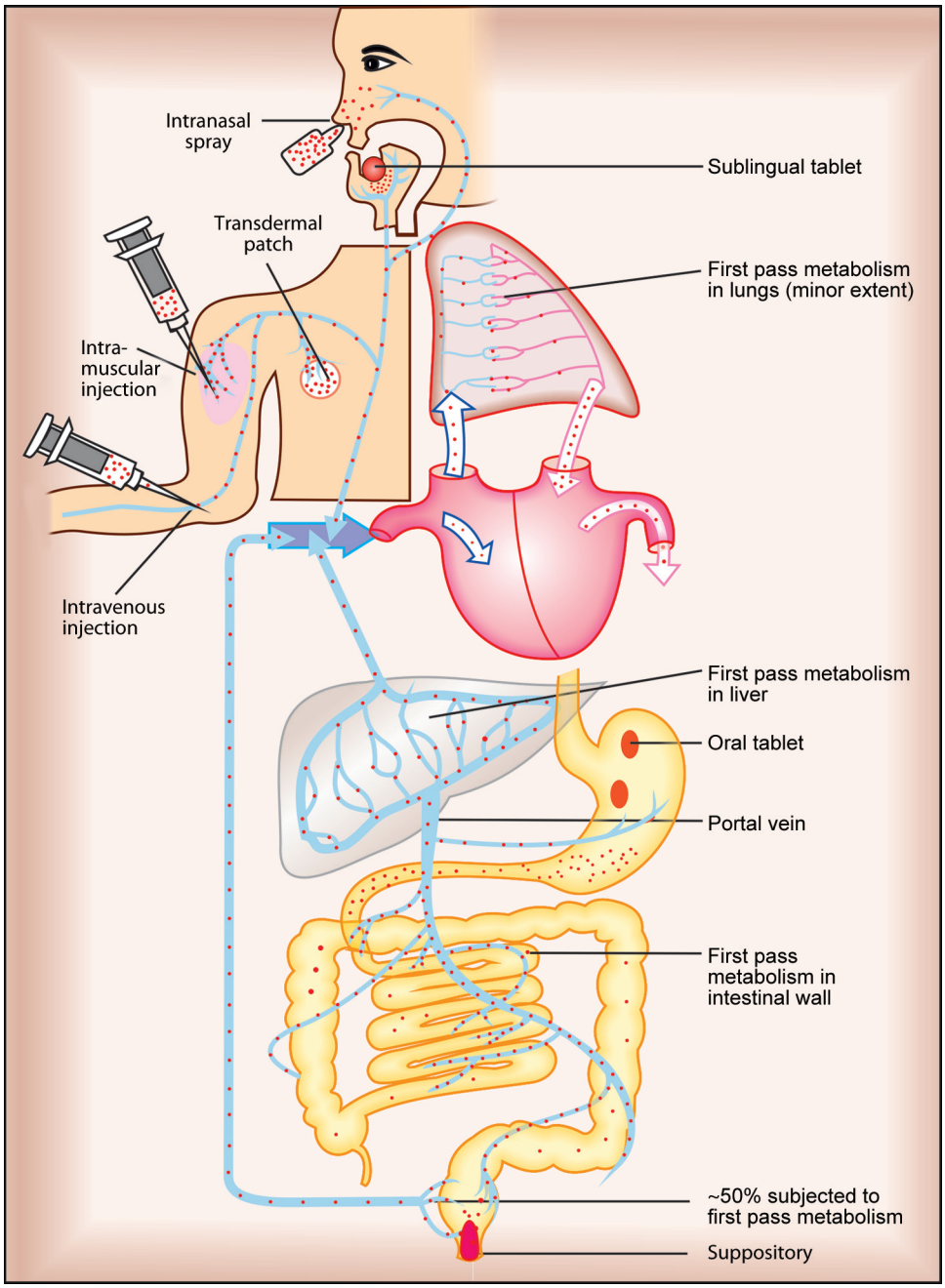

Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration and sites of first pass metabolism

Note: All 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.

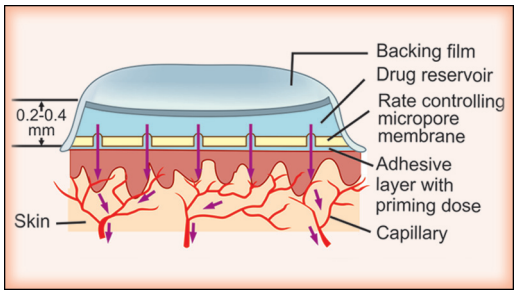

Fig. 1.2: Illustration of a transdermal drug delivery system

recurrent vomiting. However, it is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable, though diazepam solution and paracetamol suppository are dependably absorbed from 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 cm2) which deliver the contained drug at a constant rate into 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 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: usually chest, abdomen, upper arm, lower back, buttock or mastoid region are utilized.

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.

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 (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 directly reaches into the bloodstream and effects are produced immediately (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 hazards 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, 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,

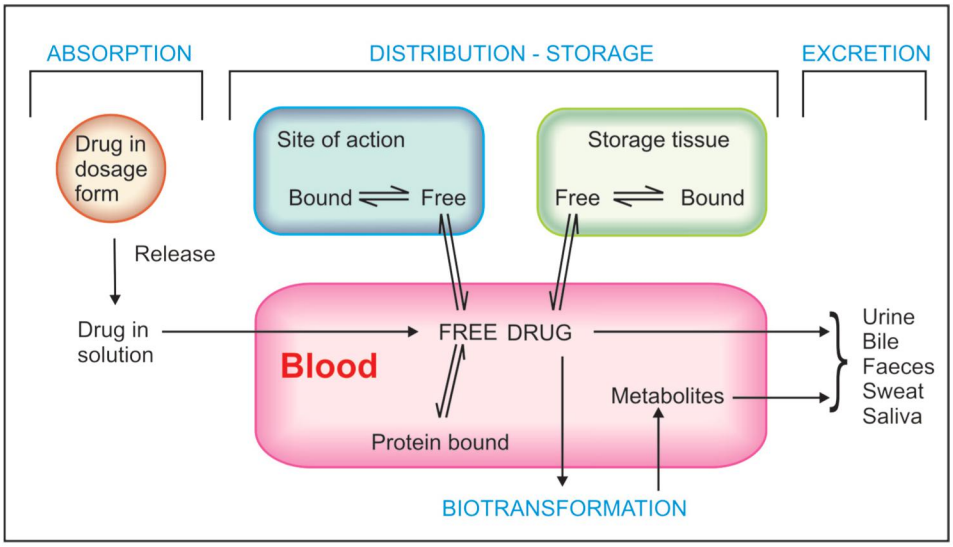

Fig. 2.1: Schematic depiction of pharmacokinetic processes

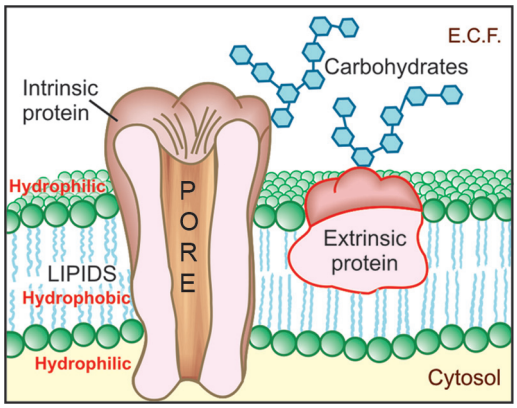

Fig. 2.2: Illustration of the organisation of biological membrane

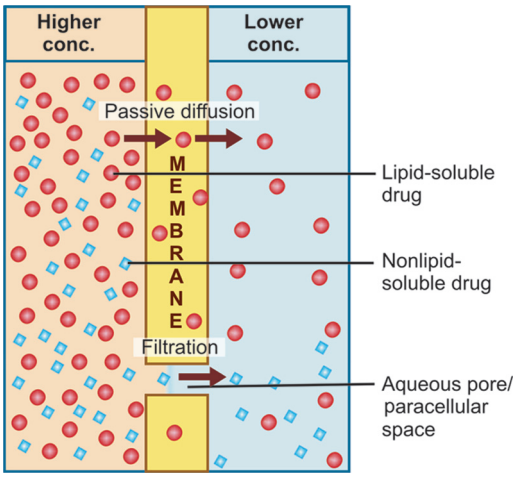

Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

carrier, receptor or signal transduction properties.

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, the membrane playing no active role in the process. This is the most important mechanism for majority of drugs; 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 lipid : water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Also, 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 more at alkaline pH and 1 scale change in pH causes 10-fold change in ionization.

Weakly basic drugs, which form salts with anions, e.g. atropine sulfate, ephedrine HCl, chloroquine phosphate, etc. conversely ionize more at acidic pH. Ions being lipid insoluble, do not diffuse and a pH difference across a membrane can cause differential distribution of weakly acidic and weakly basic drugs on the two sides (Fig. 2.4).

Implications of this consideration are:

(a) Acidic drugs, e.g. aspirin (pKa 3.5) are largely unionized at acid gastric pH and are absorbed from stomach, while bases, e.g. atropine (pKa 10) are largely ionized and are absorbed only when they reach the intestines.

(b) The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell, reverts to the ionized form within the cell (pH 7.0) and then only slowly passes to the extracellular fluid. This is called ion trapping, i.e. a weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily. This may contribute to gastric mucosal cell damage caused by aspirin.

(c) Basic drugs attain higher concentration intracellularly (pH 7.0 vs 7.4 of plasma).

(d) Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

Lipid-soluble nonelectrolytes (e.g. ethanol, diethyl-ether) readily cross biological membranes and their transport is pH independent.

Filtration

Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occurring under hydrostatic or osmotic pressure gradient, e.g. across most capillaries including glomeruli. Lipid-insoluble drugs

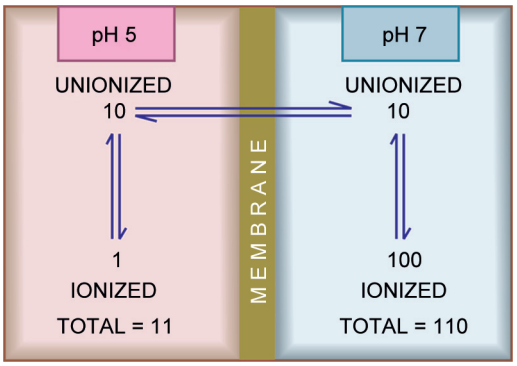

Fig. 2.4: Influence of pH difference on two sides of a biological membrane on the distribution of a weakly acidic drug with *pKa* = 6

cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores (Fig. 2.3). Majority of cells (intestinal mucosa, RBC, etc.) have very small pores (4 Å) and drugs with MW > 100 or 200 are not able to penetrate. However, capillaries (except those in brain) have large paracellular spaces (40 Å) and most drugs (even albumin) can filter through these (see Fig. 2.8A). As such, diffusion of drugs across capillaries is dependent on rate of blood flow through them rather than on lipid-solubility of the drug or pH of the medium.

Specialized transport

This can be carrier mediated or by pinocytosis.

Carrier transport

All cell membranes express a host of transmembrane proteins which serve as carriers or transporters for physiologically important ions, nutrients, metabolites, transmitters, etc. across the membrane. At some sites, certain transporters also translocate xenobiotics, including drugs and their metabolites. In contrast to channels, which open for a finite time and allow passage of specific ions, transporters combine transiently with their substrate (ion or organic

compound)—undergo a conformational change carrying the substrate to the other side of the membrane where the substrate dissociates and the transporter returns back to its original state (Fig. 2.5). Carrier transport is specific for the substrate (or the type of substrate, e.g. an organic anion), saturable, competitively inhibited by analogues which utilize the same transporter, and is much slower than the flux through channels. Depending on requirement of energy, carrier transport is of two types:

a. *Facilitated diffusion* The transporter, belonging to the super-family of solute carrier (SLC) transporters, operates passively without needing energy and translocates the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration (Fig. 2.5A). It mearly facilitates permeation of a poorly diffusible substrate, e.g. the entry of glucose into muscle and fat cells by the glucose transporter GLUT 4.

b. *Active transport* It requires energy, is inhibited by metabolic poisons, and transports the solute against its electrochemical gradient (low to high), resulting in selective accumulation of the substance on one side of the membrane. Drugs related to normal metabolites can utilize the transport processes meant for these, e.g. levodopa and methyl dopa are actively absorbed from the gut by the aromatic amino acid transporter. In addition, the body has developed some relatively nonselective transporters, like P-glycoprotein (P-gp), to deal with xenobiotics. Active transport can be primary or secondary depending on the source of the driving force.

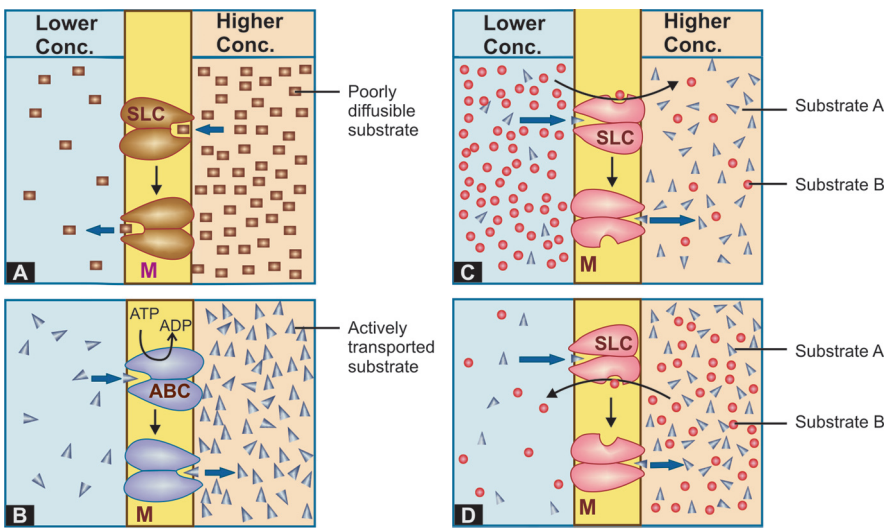

Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane
ABC—ATP-binding cassettee transporter; SLC—Solute carrier transporter; M—Membrane

A. *Facilitated diffusion:* The carrier (SLC) binds and moves the poorly diffusible substrate along its concentration gradient (high to low) and does not require energy
B. *Primary active transport:* The carrier (ABC) derives energy directly by hydrolysing ATP and moves the substrate against its concentration gradient (low to high)
C. *Symport:* The carrier moves the substrate 'A' against its concentration gradient by utilizing energy from downhill movement of another substrate 'B' in the same direction
D. *Antiport:* The carrier moves the substrate 'A' against its concentration gradient and is energized by the downhill movement of another substrate 'B' in the opposite direction

i. Primary active transport Energy is obtained directly by the hydrolysis of ATP (Fig. 2.5B). The transporters belong to the superfamily of ATP binding cassettee (ABC) transporters whose intracellular loops have ATPase activity.

P-glycoprotein is the most well known primary active transporter. Others of pharmacological significance are multidrug resistance associated protein 2 (MRP 2) and breast cancer resistance protein (BCRP).

ii. Secondary active transport In this type of active transport effected by another set of SLC transporters, the energy to pump one solute is derived from the downhill movement of another solute (mostly Na^+). When the concentration gradients are such that both the solutes move in the same direction (Fig. 2.5C), it is called *symport* or *cotransport*, but when they move in opposite directions (Fig. 2.5D), it is termed *antiport* or *exchange transport*. Metabolic energy (from hydrolysis of ATP) is spent in maintaining high transmembrane electrochemical gradient of the second solute.

The organic anion transporting polypeptide (OATP) and organic cation transporter (OCT), highly expressed in liver canaliculi and renal tubules, are secondary active transporters important in the metabolism and excretion of drugs and metabolites (especially glucuronides). The Na^+,Cl^- dependent neurotransmitter transporters for norepinephrine, serotonin and dopamine (NET, SERT and DAT) are active SLC transporters that are targets for action of drugs like tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), cocaine, etc.

Pinocytosis It is the process of transport across the cell in particulate form by formation of vesicles. This is applicable to proteins and other big molecules, and contributes little to transport of most drugs except few.

ABSORPTION

Absorption is the movement of drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles. Other factors affecting absorption are:

Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase before they are absorbed. For poorly water-soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

Concentration Passive transport depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface Larger it is, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow hastens drug absorption just as wind hastens drying of clothes.

Route of administration This affects drug absorption, because each route has its own peculiarities.

Oral

The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal. Nonionized lipid-soluble drugs, e.g. ethanol are readily absorbed from stomach as well as intestine at rates proportional to their lipid : water partition coefficient. Acidic drugs, e.g. salicylates, barbiturates, etc. are predominantly unionized in the acid gastric juice and are absorbed from stomach, while basic drugs, e.g. morphine, quinine, etc. are largely ionized and are absorbed only on reaching the duodenum. However, even for acidic drugs absorption from stomach is slower, because the mucosa is thick, covered with mucus and the surface area is small. Thus, faster gastric emptying accelerates drug absorption in general. Dissolution is a surface phenomenon, therefore, particle size

of the drug in solid dosage form governs rate of dissolution and in turn rate of absorption.

Presence of food dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk. Moreover, food delays gastric emptying. Thus, most drugs are absorbed better if taken in empty stomach. However, there are some exceptions, e.g. fatty food enhances absorption of lumefantrine. Highly ionized drugs, e.g. gentamicin, neostigmine, are practically not absorbed when given orally.

Certain drugs are degraded in the gastrointestinal tract, e.g. penicillin G by acid, insulin by peptidases, and are ineffective orally. Enteric coated tablets (having acid resistant coating) and sustained release preparations (drug particles coated with slowly dissolving material) can be used to overcome acid lability, gastric irritancy and brief duration of action.

Oral absorption of certain drugs like digoxin, cyclosporine is limited, because a fraction of the absorbed drug is extruded back into the intestinal lumen by the efflux transporter P-gp located in the gut epithelium.

Absorption of a drug can be affected by other concurrently ingested drugs. This may be a *luminal effect:* formation of insoluble complexes, e.g. tetracyclines, iron preparations with calcium salts and antacids, or ciprofloxacin with sucralfate. This interaction can be minimized by administering the two drugs at 2–3 hour intervals. Alteration of gut flora by antibiotics may disrupt the enterohepatic cycling of oral contraceptives and digoxin. Drugs can also alter absorption by gut wall effects: altering motility (anticholinergics, tricyclic antidepressants, opioids, metoclopramide) or causing mucosal damage (neomycin, methotrexate, vinblastine).

Subcutaneous and intramuscular

By these routes the drug is deposited directly in the vicinity of the capillaries. Lipid-soluble drugs pass readily across the whole surface of the capillary endothelium. Capillaries being highly porous do not obstruct absorption of even large lipid-insoluble molecules or ions (see Fig. 2.8A). Very large molecules are absorbed through lymphatics. Thus, many drugs not absorbed orally are absorbed parenterally. Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/predictable than oral absorption. Application of heat and muscular exercise accelerate drug absorption by increasing blood flow, while vasoconstrictors, e.g. adrenaline injected with the drug (local anaesthetic) retard absorption. Many depot preparations, e.g. benzathine penicillin, depot progestins, etc. can be given by these routes.

Topical sites (skin, cornea, mucous membranes)

Systemic absorption after topical application depends primarily on lipid solubility of drugs. However, only few drugs significantly penetrate intact skin. Glyceryl trinitrate, fentanyl and estradiol (*see* p. 12) have been used in this manner. Absorption can be promoted by rubbing the drug incorporated in an olegenous base or by use of occlusive dressing which increases hydration of the skin. Organophosphate insecticides coming in contact with skin can produce systemic toxicity. Abraded surfaces readily absorb drugs.

Cornea is permeable to lipid soluble, unionized physostigmine but not to highly ionized neostigmine. Similarly, mucous membranes of mouth, rectum, vagina absorb lipophilic drugs.

BIOAVAILABILITY

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2.6). It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form. Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because—

(a) The drug may be incompletely absorbed.
(b) The absorbed drug may undergo first pass metabolism in intestinal wall/liver or be excreted in bile.

Incomplete bioavailability after s.c. or i.m. injection is less common, but may occur due to local binding of the drug.

Bioequivalence Oral formulation of a drug from different manufacturers or different batches from the same manufacturer may have the same amount of the drug (chemically equivalent) but may not yield the same blood levels—*biologically inequivalent*. Two preparations of a drug are considered bioequivalent when the rate and extent of bioavailability of the active drug from them is not significantly different under suitable test conditions.

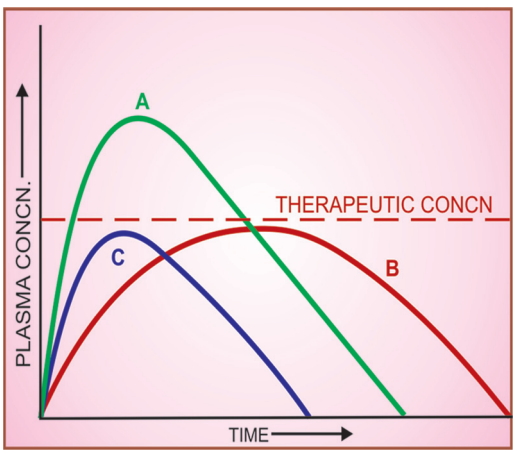

Fig. 2.6: Plasma concentration-time curves depicting bioavailability differences between three preparations of a drug containing the same amount
Note that formulation B is more slowly absorbed than A, and though ultimately both are absorbed to the same extent (area under the curve same), B may not produce therapeutic effect; C is absorbed to a lesser extent—lower bioavailability.

Before a drug administered orally in solid dosage form can be absorbed, it must break into individual particles of the active drug (disintegration). Tablets and capsules contain a number of other materials—diluents, stabilizing agents, binders, lubricants, etc. The nature of these as well as details of the manufacture process, e.g. force used in compressing the tablet, may affect disintegration. The released drug must then dissolve in the aqueous gastrointestinal contents. The rate of dissolution is governed by the inherent solubility, particle size, crystal form and other physical properties of the drug. Differences in bioavailability may arise due to variations in disintegration and dissolution rates.

Differences in bioavailability are seen mostly with poorly soluble and slowly absorbed drugs. Reduction in particle size increases the rate of absorption of aspirin (microfine tablets). The amount of griseofulvin and spironolactone in the tablet can be reduced to half if the drug particle is microfined. There is no need to reduce the particle size of freely water-soluble drugs, e.g. paracetamol.

Bioavailability variation assumes practical significance for drugs with low safety margin (digoxin) or where dosage needs precise control (oral hypoglycaemics, oral anticoagulants). It may also be responsible for success or failure of an antimicrobial regimen.

However, for a large number of drugs bioavailability differences are negligible and the risks of changing branded to generic product or to another brand of the same drug have often been exaggerated.

DISTRIBUTION

Once a drug has gained access to the bloodstream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent of distribution of a drug depends on its:

- lipid solubility,
- ionization at physiological pH (dependent on pKa),
- extent of binding to plasma and tissue proteins and
- differences in regional blood flow.

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and in the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V)

Presuming that the body behaves as a single homogeneous compartment with volume V into which the drug gets immediately and uniformly distributed

$$V = \frac{\text{Dose administered i.v.}}{\text{Plasma concentration}} \quad ...(3)$$

Since in the example shown in Fig. 2.7 the drug does not actually distribute into 20 L of body water, with the exclusion of the rest of it, this is only an apparent volume of distribution which can be defined as "the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma." Thus, it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma. Considered together with drug clearance, this is a very useful pharmacokinetic concept.

Lipid-insoluble drugs do not enter cells—V approximates extracellular fluid volume, e.g. streptomycin, gentamicin 0.25 L/kg.

Distribution is not only a matter of dilution but also binding and sequestration. Drugs extensively bound to plasma proteins

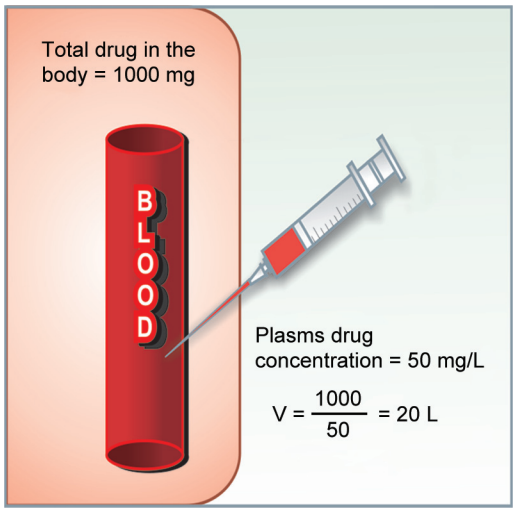

Fig. 2.7: Illustration of the concept of apparent volume of distribution (V)

In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L.

are largely restricted to the vascular compartment and have low values, e.g. diclofenac and warfarin (99% bound) V = 0.15 L/kg.

Drugs sequestrated in other tissues may have V much more than total body water or even body mass, e.g. digoxin 6 L/kg, chlorpromazine 25 L/kg, morphine 3.5 L/kg, because most of the drug is present in other tissues, and plasma concentration is low.

Pathological states, e.g. congestive heart failure, uraemia, cirrhosis of liver, etc. can alter the V of many drugs by altering distribution of body water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

Factors governing volume of drug distribution

- Lipid : water partition coefficient of the drug
- pKa value of the drug
- Degree of plasma protein binding
- Affinity for different tissues
- Fat : lean body mass ratio
- Diseases like CHF, uraemia, cirrhosis

Redistribution Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc. Later, less vascular but more bulky tissues (muscle, fat) take up the drug—plasma concentration falls and the drug is withdrawn from brain, etc. If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action. Greater the lipid solubility of the drug, faster is its redistribution. Anaesthetic action of thiopentone injected i.v. is terminated in a few minutes due to redistribution. A relatively short (6-8 hr) hypnotic action due to redistribution is exerted by oral diazepam or nitrazepam despite their elimination half-life of > 30 hr. However, when the same drug is given repeatedly or by continuous i.v. infusion over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

Penetration into brain and CSF The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, an investment of neural tissue (Fig. 2.8B) covers the capillaries. Together they constitute the so-called *blood-brain barrier* (BBB). A similar *blood-CSF barrier* is located in the choroid plexus where capillaries are lined by choroidal epithelium having tight junctions. Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs, e.g. gentamicin, neostigmine, etc. Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system. Efflux transporters like P-glycoprotein present in brain and choroidal vessels extrude many drugs that enter brain by other processes. Dopamine does not enter brain, but its precursor levodopa does; as such, the latter is used in parkinsonism. Inflammation of meninges or brain increases permeability of these barriers.

There is also an enzymatic BBB: monoamine oxidase (MAO), cholinesterase and some other enzymes are present in the capillary walls or in the cells lining them. They do not allow catecholamines, 5-HT, acetylcholine, etc. to enter brain in the active form.

The BBB is deficient at the CTZ in the medulla oblongata (even lipid-insoluble drugs are emetic) and at certain periventricular sites—(anterior hypothalamus). Exit of drugs from the CSF and brain, however, is not dependent on lipid solubility and is rather unrestricted.

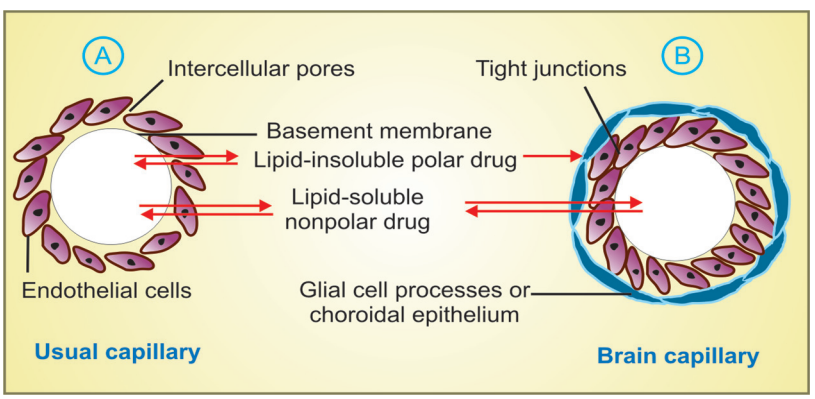

Fig. 2.8: Passage of drugs across capillaries

A. Usual capillary with large paracellular spaces through which even large lipid-insoluble molecules diffuse
B. Capillary constituting blood-brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial processes or choroidal epithelium do not allow passage of nonlipid-soluble molecules/ions

Bulk flow of CSF (along with the drug dissolved in it) occurs through the arachnoid villi. Further, nonspecific organic ion transport processes (similar to those in renal tubule) operate at the choroid plexus.

Passage across placenta Placental membranes are lipoidal and allow free passage of lipophilic drugs while restricting hydrophilic drugs. The placental efflux P-glycoprotein also serves to limit foetal exposure to maternally administered drugs. Placenta is a site for drug metabolism as well. However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the new-born (drug taken just before delivery, e.g. morphine).

Plasma protein binding

Most drugs possess physicochemical affinity for plasma proteins. Acidic drugs generally bind to plasma albumin and basic drugs to a1 acid glycoprotein. Binding to albumin is quantitatively more important. Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding), for example:

Flurazepam	10%	Alprazolam	70%
Lorazepam	90%	Diazepam	99%

Increasing concentrations of the drug can progressively saturate the binding sites; fractional binding may be lower when large amounts of the drug are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentrations of a drug. The clinically significant implications of plasma protein binding are:

(i) Highly plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volumes of distribution.

(ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination. Plasma protein binding thus tantamounts to temporary storage of the drug.

(iii) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or kidney tubules. Glomerular filtration does not reduce the concentration of the free form in the efferent vessels because water is also filtered. Active tubular secretion, however, removes the drug without the attendant solvent → concentration of free drug falls → bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow (See Fig. 2.10). The same is true of active transport of highly extracted drugs in liver. Plasma protein binding in this situation acts as a carrier mechanism and hastens drug elimination, e.g. excretion of penicillin; metabolism of lidocaine. Highly protein bound drugs are not removed by haemodialysis and need special techniques for treatment of poisoning.

(iv) The generally expressed plasma concentrations of the drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these to concentrations of the drug that are active in vitro, e.g. MIC of an antimicrobial.

Drugs highly bound to plasma protein

To Albumin	*To α_1-acid glycoprotein*
Barbiturates	b-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lignocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Warfarin	Verapamil