4th Edition

Essentials of Pharmacology for Dentistry

Covering the latest curriculum

KD Tripathi

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Essentials of Pharmacology for Dentistry

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4th Edition

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JAYPEE BROTHERS MEDICAL PUBLISHERS
The Health Sciences Publisher
New Delhi | London

Jaypee Brothers Medical Publishers (P) Ltd

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Website: www.jaypeedigital.com

Managing Editor: M Tripathi

Essentials of Pharmacology for Dentistry

First Edition: 2005
Second Edition: 2011
Third Edition: 2016
Fourth Edition: **2021**

ISBN 978-93-5090-420-6

Printed at

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**

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
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 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. 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.

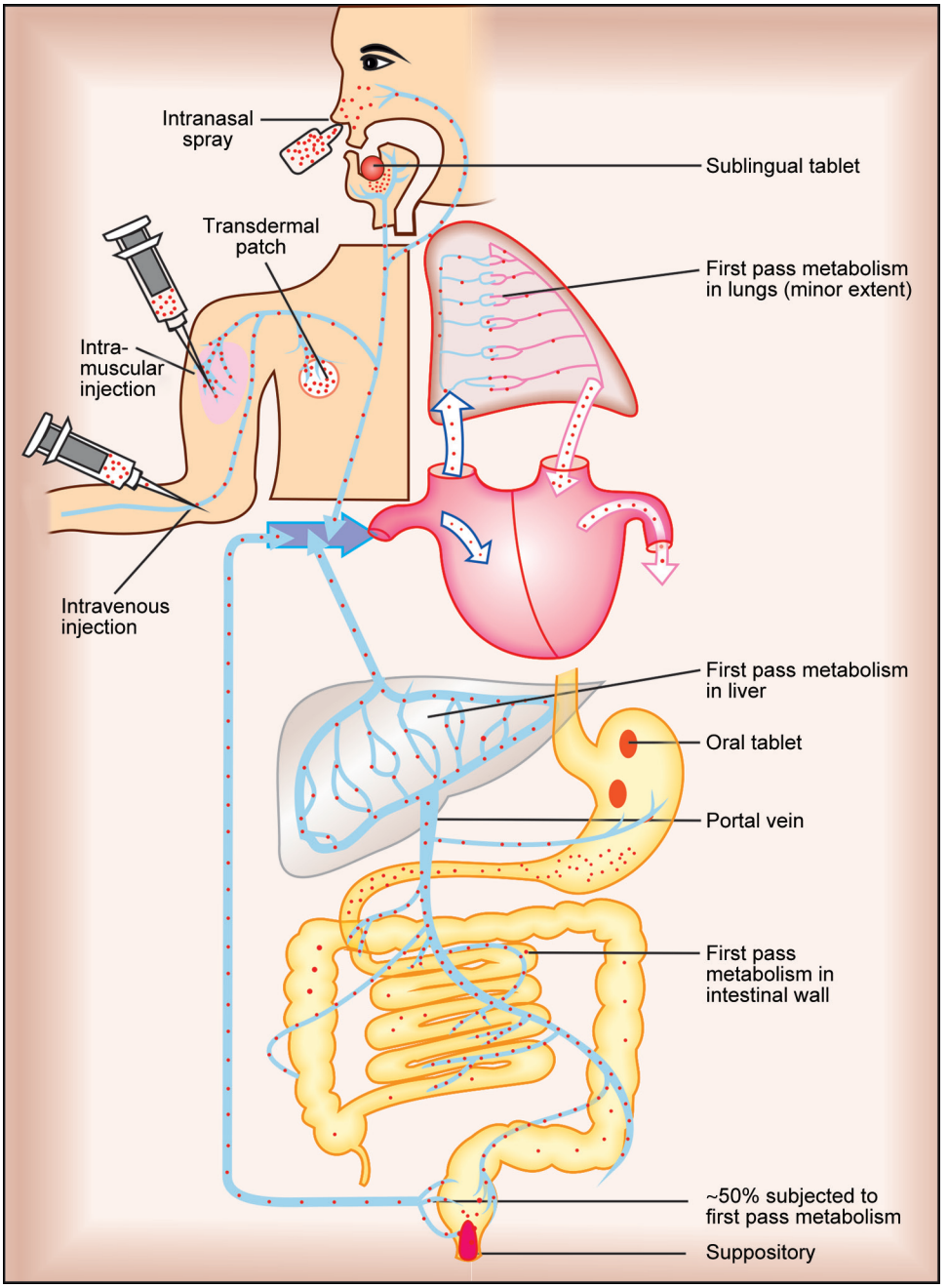

Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration, and sites of first pass metabolism

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.

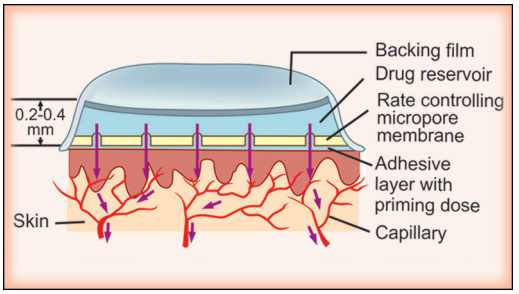

Fig. 1.2: Illustration of a transdermal drug delivery system

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,

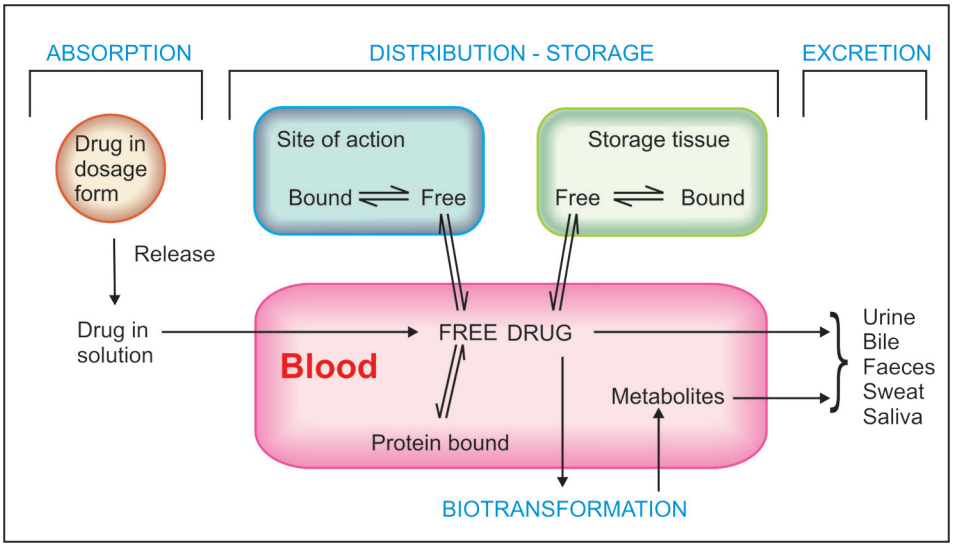

Fig. 2.1: Schematic depiction of pharmacokinetic processes

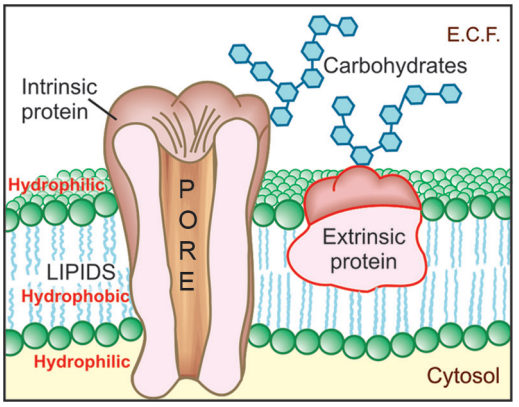

Fig. 2.2: Illustration of the organization of biological membrane

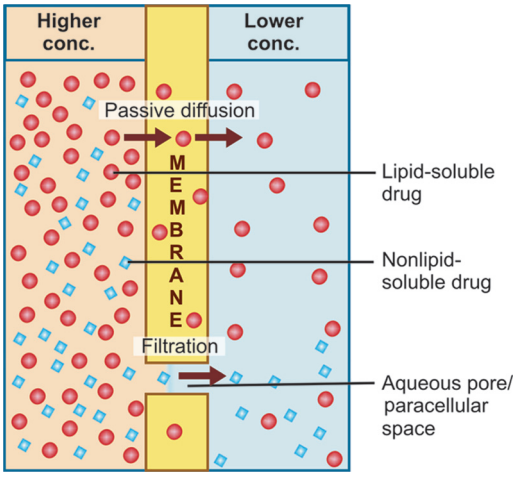

Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

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

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 the 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 (where pH is 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

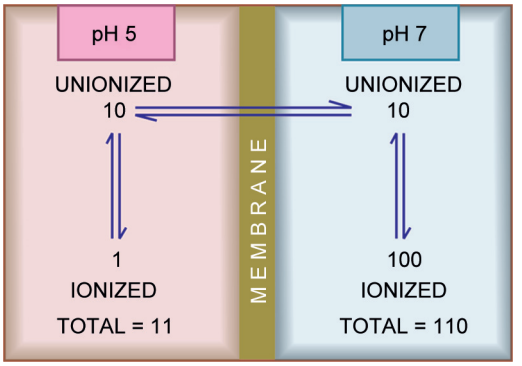

Fig. 2.4: Influence of pH difference on two sides of a biological membrane on the distribution of a weakly acidic drug with *pKa* = 6

including glomeruli. Lipid-insoluble drugs 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 vesicular transport (endocytosis and exocytosis).

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 merely 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.

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 cassette (ABC) transporters whose intracellular loops have ATPase activity.

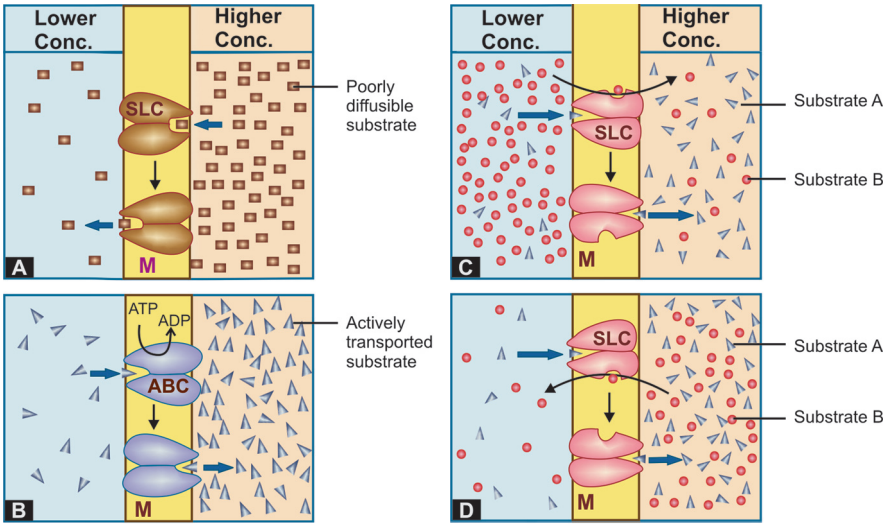

Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane
ABC—ATP-binding cassette transporter; SLC—Solute carrier transporter; M—Membrane

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

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.

Vesicular transport (endocytosis, exocytosis)

Certain substances with very large or impermeable molecules are transported inside the cell (*endocytosis*) or extruded from it (*exocytosis*) by enclosing their particles into tiny vesicles. A binding protein located on the membrane complexes with the substance and initiates vesicle formation (Fig. 2.6). The vesicle then detaches from the membrane and may remain stored within the cell, or it may release the substance in the cytoplasm, or it may move to the opposite membrane, fuse with it to release the substance across the cell (exocytosis).

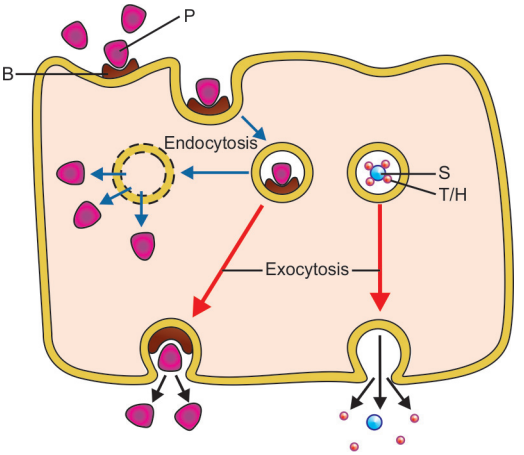

Fig. 2.6: Illustration of vesicular transport (endocytosis and exocytosis).
Endocytosis: The large molecular particle (P) binds to a binding protein (B) on the surface of the cell. The membrane invaginates to form a vesicle. The vesicle may remain stored within the cell, or it may disintegrate to release the substance in the cytoplasm, or be extruded across the cell by exocytosis.
Exocytosis: The particle or the transmitter/hormone (T/H) stored within intracellular vesicles, generally as a complex with a storage protein (S), is secreted by exocytosis.

Vesicular transport is applicable to proteins and other big molecules, and contributes little to transport of most drugs, barring few like vit B_{12} which is absorbed from the gut after binding to intrinsic factor (a protein). Most hormones (insulin, etc.) and neurotransmitters, like noradrenaline, are secreted/released from the cell/nerve ending by exocytosis.

ABSORPTION OF DRUGS

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 the 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. Moreover, certain drugs form poorly absorbed complexes with food constituents, e.g. tetracyclines with calcium present in milk. In addition, 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 gastric 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 with a gap of 2–3 hours. 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 retard motility, while metoclopramide enhances it) 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. 2.9A). 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 the drug. However, only few drugs significantly penetrate intact skin. Glyceryl trinitrate, fentanyl, nicotine, testosterone and estradiol (*see* p. 11) 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 administered by any route, as determined by its concentration-time curve in blood or by its excretion in urine (Fig. 2.7). 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

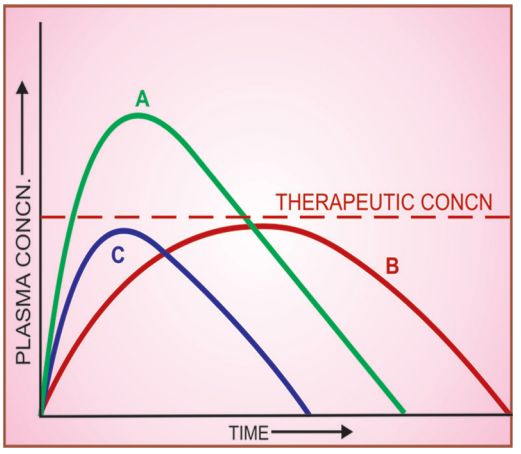

Fig. 2.7: Plasma concentration-time curves depicting bioavailability differences between three preparations of a drug containing the same amount
Note that formulation B is more slowly absorbed than A, and though ultimately both are absorbed to the same extent (area under the curve same), B may not produce therapeutic effect after a single dose. However, average blood levels may be similar with both A and B formulations when repeated doses are given. C is absorbed to a lesser extent—lower bioavailability.

(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.

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, in the case of 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 OF DRUGS

Once a drug has gained access to the bloodstream, it diffuses 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 and its pattern of tissue distribution 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 from the vascular compartment 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

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}} \quad \ldots(3)$$

Since in the example shown in Fig. 2.8 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

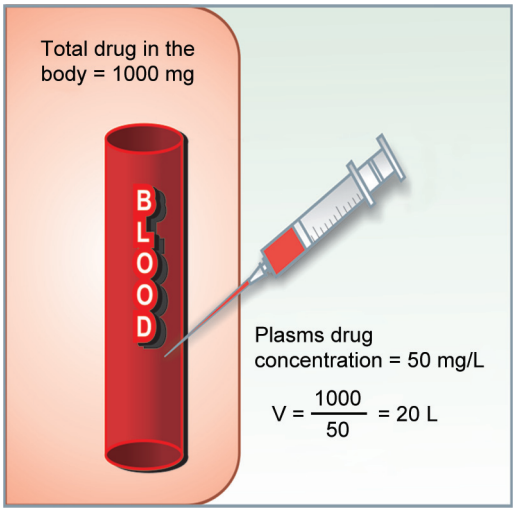

Fig. 2.8: Illustration of the concept of apparent volume of distribution (V)

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.

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 are largely restricted to the vascular compartment and have low values of *V*, 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. 2.9B) 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

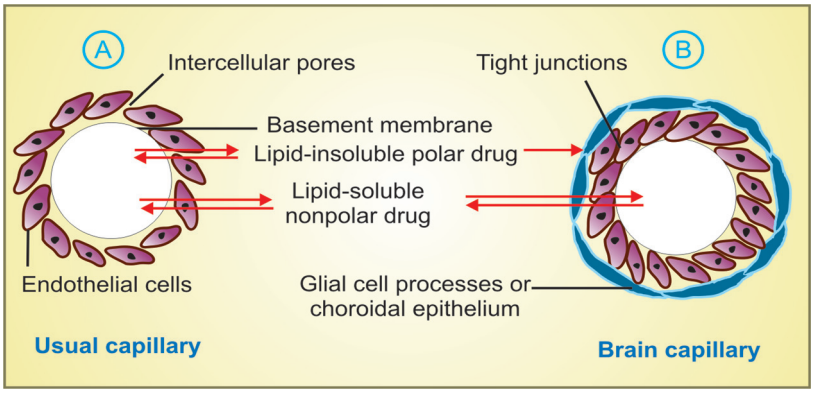

Fig. 2.9: Passage of drugs across capillaries

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

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. This is due to bulk flow of CSF (along with the drug dissolved in it) back into the blood 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 α1 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

Drugs highly bound to plasma protein	
To Albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Warfarin	Verapamil

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. 2.12). The same is true of active transport of highly extracted drugs in the 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.

(v) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s); the drug bound with higher affinity will displace the one bound with lower affinity and tend to raise the concentration of its free form. This, however, is often transient because the displaced drug will diffuse into the tissues as well as get metabolized or excreted; the new steady-state free drug concentration is only marginally higher unless the displacement extends to tissue binding or there is concurrent inhibition of metabolism and/or excretion reducing drug clearance. The overall impact of many displacement interactions is minimal; except when the interaction is more complex. Moreover, two highly bound drugs do not necessarily displace each other—their binding sites may not overlap, e.g. probenecid and indomethacin are highly bound to albumin but do not displace each other. Similarly, acidic drugs do not generally displace basic drugs and vice versa.

(vi) In hypoalbuminaemia, binding may be reduced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease (acute phase reactant α1 acid-glycoprotein increases).

Tissue storage Drugs may also accumulate in specific organs or get bound to specific tissue constituents (*see* box).

Drugs sequestrated in various tissues are distributed unequally, tend to have larger volume of distribution and longer duration of action. Some may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, emetine on heart and skeletal muscle. Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei.

Drugs concentrated in tissues		
Skeletal muscle, heart	—	Digoxin, emetine (bound to muscle proteins)
Liver	—	Chloroquine, tetracyclines, emetine, digoxin
Kidney	—	Digoxin, chloroquine, emetine
Thyroid	—	Iodine
Brain	—	Chlorpromazine, acetazolamide, isoniazid
Retina	—	Chloroquine (bound to nucleoproteins)
Iris	—	Ephedrine, atropine (bound to melanin)
Bone and teeth	—	Tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite)
Adipose tissue	—	Thiopentone, ether, minocycline, DDT dissolve in neutral fat due to high lipid solubility; remain stored due to poor blood supply of fat

BIOTRANSFORMATION (Metabolism) OF DRUGS

Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid soluble) compounds polar (lipid insoluble) so that they are not reabsorbed in the renal tubules and are excreted. Most hydrophilic drugs, e.g. gentamicin, neostigmine, etc. are not biotransformed and are excreted unchanged.

The primary site for drug metabolism is liver; others are—kidney, intestine, lungs and plasma. Biotransformation of drugs may lead to the following.

(i) Inactivation Most drugs and their active metabolites are rendered inactive or less active by metabolism, e.g. lidocaine, ibuprofen, paracetamol, chloramphenicol, propranolol and its active metabolite 4-hydroxypropranolol.

(ii) Active metabolite from an active drug Many drugs have been found to be partially converted to one or more active metabolite (*see* box); the effects observed are the sum total of that due to the parent drug and its active metabolite(s).

(iii) Activation of inactive drug Few drugs are inactive as such and need conversion in the body to one or more active metabolite(s). Such a drug is called a *prodrug* (*see* box). The prodrug may offer advantages over the active form in being more stable, having better bioavailability or other desirable pharmacokinetic properties or less side effects and toxicity. Some prodrugs are activated selectively at the site of action.

Active drug		Active metabolite
Allopurinol	—	Alloxanthine
Procainamide	—	N-acetyl-procainamide
Primidone	—	Phenobarbitone, phenylethylmalonamide
Cefotaxime	—	Deacetyl cefotaxime
Diazepam	—	Desmethyl-diazepam, oxazepam
Imipramine	—	Desipramine
Amitriptyline	—	Nortriptyline
Codeine	—	Morphine
Morphine	—	Morphine-6-glucuronide
Spironolactone	—	Canrenone
Losartan	—	E 3174

Biotransformation reactions can be classified into:

(a) Nonsynthetic/Phase I reactions: a functional group (–OH, –COOH, –CHO, $–NH_2$, –SH, etc.) may be generated/exposed. The metabolite may be active or inactive.

Prodrug		Active form
Levodopa	—	Dopamine
Enalapril	—	Enalaprilat
α-Methyldopa	—	α-Methylnorepinephrine
Clopidogrel	—	Thiol metabolite
Dipivefrine	—	Epinephrine
Proguanil	—	Cycloguanil
Sulfasalazine	—	5-Aminosalicylic acid
Acyclovir	—	Acyclovir triphosphate
Cyclophosphamide	—	Aldophosphamide, phosphoramide mustard, acrolein
Mercaptopurine	—	Methylmercaptopurine ribonucleotide

(b) Synthetic/Conjugation/Phase II reactions: an endogenous radical is conjugated to the drug. The metabolite is mostly inactive, except few drugs, e.g. morphine-6-glucuronide.

Nonsynthetic reactions

(i) Oxidation This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are: hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation, oxidative deamination, etc.

In many cases, the initial insertion of oxygen atom into the drug molecule produces short lived highly reactive quinone/epoxide/superoxide intermediates which then convert to more stable compounds.

Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and molecular O_2. More than 100 cytochrome P-450 (CYP-450) isoenzymes differing in their affinity for various substrates (drugs), have been identified. The CYP-450 isoenzymes important for drug metabolism in humans, along with their clinically relevant substrate drugs, inhibitors and inducers are listed in Table 2.1.

The relative amount of different cytochrome P-450s differs among species and among individuals of the same species. These differences largely account for the marked interspecies and interindividual differences in rate of metabolism of drugs.

(ii) *Reduction* This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction. Drugs primarily reduced are chloramphenicol, halothane and warfarin.

(iii) *Hydrolysis* This is cleavage of drug molecule by taking up a molecule of water.

$$\text{Ester} + H_2O \xrightarrow{esterase} \text{Acid} + \text{Alcohol}$$

Similarly, amides and polypeptides are hydrolyzed by amidases and peptidases. Hydrolysis occurs in liver, intestines, plasma and other tissues. Examples are choline esters, procaine, lidocaine, procainamide, indomethacin, pethidine, oxytocin.

Synthetic reactions

These reactions involve conjugation of the drug or its phase I metabolite with an endogenous substrate, usually derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile.

(i) *Glucuronide conjugation* This is the most important synthetic reaction carried out by a group of UDP-glucuronosyl transferases (UGTs). Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. Examples are chloramphenicol, aspirin, diazepam, morphine, metronidazole. Not only drugs but endogenous substrates like bilirubin, steroidal hormones and thyroxine utilize this pathway. Glucuronidation favours excretion of the drug in bile. Drug glucuronides excreted in bile can be hydrolyzed by bacteria in the gut—the liberated drug is

Table 2.1: Major drug metabolizing CYP450 isoenzymes in humans with their important substrate drugs, inhibitors and inducers

CYP-450 isoenzyme	*Drugs metabolized*	*Inhibitors*	*Inducers*
CYP3A4 CYP3A5	Losartan, Carbamazepine Hydrocortisone Paracetamol, Diazepam Buspirone, Mifepristone Ritonavir, Saquinavir Simvastatin, Quinidine Verapamil, Lidocaine Dapsone, Nevirapine	Erythromycin Clarithromycin Ketoconazole Itraconazole Verapamil Ritonavir Fluoxetine Grape fruit juice	Barbiturates Phenytoin Carbamazepine Rifampin Glucocorticoids Nevirapine
CYP2D6	Metoprolol, Debrisoquine Nebivolol, Amitryptyline Clomipramine, Fluoxetine Paroxetine, Venlafaxine Haloperidol, Clozapine Risperidone, Codeine Propafenone, Flecainide	Qunidine Fluoxetine Paroxetine	Phenobarbitone Rifampin
CYP2C8 CYP2C9	Phenytoin, Carbamazepine Warfarin, Tolbutamide Repaglinide, Pioglitazone Diclofenac, Ibuprofen Losartan	Fluvoxamine Fluconazole Gemfibrozil Trimethoprim	Phenobarbitone Carbamazepine Rifampin
CYP2C19	Omeprazole, Lansoprazole Amitriptyline, Citalopram Phenytoin, Diazepam Propranolol, Clopidogrel	Omeprazole Fluconazole	Carbamazepine Rifampin
CYP1A1 CYP1A2	Theophylline, Caffeine Paracetamol, Warfarin Carbamazepine	Fluvoxamine Fluoxetine	Polycyclic hydrocarbons Cigarette smoke Charbroiled meat Rifampin Carbamazepine
CYP2E1	Alcohol, Halothane Paracetamol*	Disulfiram Fomepizole	Chronic alcoholism Isoniazid
CYP2B6	Efavirenz, Nevirapine Cyclophosphamide, Methadone Sertraline, Clopidogrel	Paroxetine Sertraline Clopidogrel	Phenobarbitone Cyclophosphamide

* Generates toxic metabolite N-acetyl-p-benzoquinoneimine (NABQI)

reabsorbed and undergoes the same fate. This enterohepatic cycling of the drug prolongs its action, e.g., oral contraceptives.

(ii) *Acetylation* Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A, e.g. sulfonamides, isoniazid, PAS, dapsone, hydralazine. Multiple genes control the N-acetyl transferases (NATs) and rate of acetylation shows genetic polymorphism (slow and fast acetylators).

(iii) *Methylation* Amines and phenols can be methylated by methyl transferases; methionine and cysteine acting as methyl donors. Drugs methylated are adrenaline, histamine, nicotinic acid, methyldopa, etc.

(iv) *Sulfate conjugation* The phenolic compounds and steroids are sulfated

by sulfotransferases (SULTs), e.g. chloramphenicol, adrenal steroids and sex steroids.

(v) *Glycine conjugation* Aspirin, nicotinic acid and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

(vi) *Glutathione conjugation* Carried out by glutathione-S-transferase (GST) to form a mercapturate is normally a minor pathway. However, it serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs, e.g. paracetamol. When a large amount of such intermediates are formed (in poisoning or after enzyme induction), glutathione supply falls short—toxic adducts are formed with tissue constituents resulting in hepatic, renal and other tissue damage.

(vii) *Ribonucleoside/nucleotide synthesis* This reaction is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

Most drugs are metabolized by multiple pathways, simultaneously or sequentially as illustrated in Fig. 2.10. As such, a variety of metabolities of a drug may be produced.

Only few drugs are metabolized by enzymes of intermediary metabolism, e.g. alcohol by dehydrogenase, allopurinol by xanthine oxidase, succinylcholine and procaine by plasma cholinesterase, adrenaline by monoamine oxidase. Majority of drugs are acted on by relatively nonspecific enzymes which are directed to types of molecules rather than to specific drugs. The same enzyme can metabolize many drugs. The drug metabolizing enzymes are divided into two types:

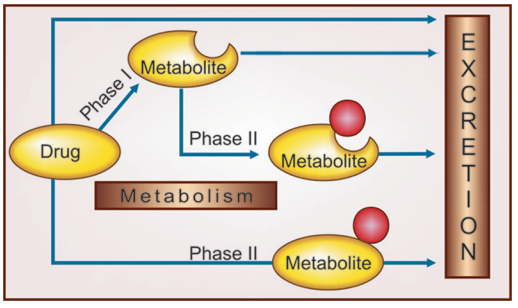

Fig. 2.10: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

Microsomal enzymes These are located on smooth endoplasmic reticulum (a system of microtubules inside the cell), primarily in liver, also in kidney, intestinal mucosa and lungs. The monooxygenases, cytochrome P 450, UGTs, epoxide hydrolases are microsomal enzymes.

These enzymes catalyze most of the oxidations, reductions, hydrolysis and glucuronide conjugation. Microsomal enzymes are inducible by a number of drugs, certain dietary constituents and other agencies.

Nonmicrosomal enzymes These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma. The esterases, amidases, some flavoprotein oxidases and most conjugases are nonmicrosomal. Reactions catalyzed are:

Some oxidations and reductions, many hydrolytic reactions and all conjugations except glucuronidation.

The nonmicrosomal enzymes are not inducible but many show genetic polymorphism (acetyl transferase, pseudocholinesterase).

Both microsomal and nonmicrosomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids. This deficit is made up in first few months, more quickly in case of oxidation and other phase I reactions than in case of glucuronide and other conjugations which take 3 or more months to reach adult levels.

The amount and kind of drug metabolizing enzymes is controlled genetically and is also altered by environmental factors. Thus, marked interspecies and interindividual differences are seen. Up to 6-fold difference in the rate of metabolism of a drug among normal human adults may be observed. This is one of the major causes of individual variation in drug response.

Hofmann elimination This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme, e.g. atracurium.

INHIBITION OF DRUG METABOLISM

Few drugs, especially azole antifungals and macrolide antibiotics bind to the heme iron in CYP450 and inhibit the metabolism of several drugs. Moreover, one drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or cofactors. However, such interactions are not as common as one would expect, because often different drugs are substrates for different CYP-450 isoenzymes. Moreover, a drug may inhibit one isoenzyme while being itself a substrate of another isoenzyme, e.g. quinidine is metabolized mainly by CYP3A4 but inhibits CYP2D6. Also most drugs, at therapeutic concentrations are metabolized by non-saturation kinetics, i.e. the enzyme is present in excess. Clinically significant inhibition of drug metabolism occurs in case of drugs having affinity for the same isoenzyme, especially if they are metabolized by saturation kinetics or if kinetics changes from first order to zero order over the therapeutic range (capacity limited metabolism). The 'boosted' HIV-protease inhibitor (PI) strategy utilizes the potent CYP3A4 inhibitory action of low-dose ritonavir to lower the dose of other PIs like atazanavir, lopinavir, etc. given concurrently. Inhibition of drug metabolism occurs in a dose-related manner and can precipitate toxicity of the object drug (whose metabolism has been inhibited).

Because enzyme inhibition occurs by direct effect on the enzyme, it has a fast time course (within hours) compared to enzyme induction (*see* below).

Metabolism of drugs with high hepatic extraction is dependent on liver blood flow, and is called blood flow limited metabolism. Propranolol reduces rate of lidocaine metabolism by decreasing hepatic blood flow.

Drugs that inhibit drug metabolizing enzymes	
Allopurinol	Amiodarone
Omeprazole	Propoxyphene
Erythromycin	Isoniazid
Clarithromycin	Cimetidine
Chloramphenicol	Quinidine
Ketoconazole	Metronidazole
Itraconazole	Disulfiram
Ciprofloxacin	Verapamil
Sulfonamides	Ritonavir
Fluoxetine	

MICROSOMAL ENZYME INDUCTION

Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and glucuronyl transferase. As a result, the rate of metabolism of inducing drug itself and/or other coadministered drugs is increased.

Different inducers are relatively selective for certain CYP450 isoenzyme families, e.g.:

- Anticonvulsants (phenytoin, carbamazepine, phenobarbitone), rifampin, glucocorticoids induce CYP3A isoenzymes.
- Phenobarbitone and rifampin also induce CYP2B1, CYP2D6 and CYP2C8/9.
- Isoniazid and chronic alcohol consumption induce CYP2E1.
- Other important enzyme inducers are chronic alcoholism, nevirapine, griseofulvin, DDT.

Since different CYP isoenzymes are involved in the metabolism of different drugs, every

inducer increases biotransformation of certain drugs but not that of others. However, phenobarbitone like inducers of CYP3A and CYP2D6 affect the metabolism of a large number of drugs, because these isoenzymes act on many drugs. On the other hand, induction by polycyclic hydrocarbons is limited to a few drugs (like theophylline, warfarin) because CYP1A isoenzyme metabolizes only few drugs.

Induction involves microsomal enzymes in liver as well as other organs and increases the rate of metabolism by 2–4-fold. Induction takes 4–14 days to reach its peak and is maintained till the inducing agent is being given. Thereafter, the enzymes return to their original value over 1 to 3 weeks.

Consequences of microsomal enzyme induction

1. Decreased intensity and/or duration of action of drugs that are inactivated by metabolism, e.g. failure of contraception with oral contraceptives and loss of anti-HIV action of nevirapine due to coadministration of rifampin.
2. Increased intensity of action of drugs that are activated by metabolism. Acute paracetamol toxicity is due to one of its metabolites—toxicity occurs at lower doses in patients receiving enzyme inducers.
3. Tolerance—if the drug induces its own metabolism (autoinduction), e.g. carbamazepine, rifampin. Nevirapine dose needs to be doubled after 2 weeks.
4. Some endogenous substrates (steroids, bilirubin) are also metabolized faster.
5. Precipitation of acute intermittent porphyria: enzyme induction increases porphyrin synthesis by derepressing d-aminolevulenic acid synthetase.
6. Intermittent use of an inducer may interfere with adjustment of dose of another drug prescribed on regular basis, e.g. oral anticoagulants, oral hypoglycaemics, antiepileptics, antihypertensives.

Drugs whose metabolism is significantly affected by enzyme induction are—phenytoin, warfarin, tolbutamide, oral contraceptives, chloramphenicol, doxycycline, theophylline, griseofulvin.

Possible uses of enzyme induction

1. Congenital nonhaemolytic jaundice: phenobarbitone causes rapid clearance of jaundice.
2. Cushing's syndrome: phenytoin may reduce the manifestations.
3. Chronic poisonings.
4. Liver disease.

FIRST PASS (PRESYSTEMIC) METABOLISM

This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation. All orally administered drugs are exposed to drug metabolizing enzymes in the intestinal wall and liver (where they first reach through the portal vein). This can be circumvented by administering the drug through sublingual, transdermal or parenteral routes. Presystemic metabolism of limited magnitude can also occur in the skin (transdermally administered drug) and in lungs (for drug reaching venous blood through any route). The extent of first pass metabolism differs for different drugs (Table 2.2) and is an important determinant of oral bioavailability.

Attributes of drugs with high first pass metabolism

(a) Oral dose is considerably higher than sublingual or parenteral dose.
(b) There is marked individual variation in the oral dose due to differences in the extent of first pass metabolism.
(c) Oral bioavailability is apparently increased in patients with severe liver disease.
(d) Oral bioavailability of a drug is increased if another drug competing with it in first pass metabolism is given concurrently, e.g. chlorpromazine and propranolol.

Table 2.2: Extent of hepatic first pass metabolism of some important drugs

Low	*Intermediate*	*High*	
		not given orally	*high oral dose*
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Tolbutamide	Quinidine	Lidocaine	Alprenolol
Theophylline	Desipramine	Hydrocortisone	Verapamil
Pindolol	Nortriptyline	Testosterone	Salbutamol
Isosorbide mononitrate	Chlorpromazine		Glyceryl trinitrate
	Pentazocine		Morphine
	Metoprolol		Pethidine

EXCRETION OF DRUGS

Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine Through the kidney. It is the most important channel of excretion for majority of drugs (see below).

2. Faeces Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Organic acids (especially drug glucuronides), organic bases and steroids are actively transported into bile by liver through separate nonspecific active transporters (OATP, MRP2, OCT, P-gP, etc.). Relatively larger molecules (MW > 300) are preferentially eliminated in the bile. Most of the unconjugated drug present in the gut, including that released by deconjugation of glucuronides by gut bacteria is reabsorbed (enterohepatic cycling *see* Fig. 2.11) and ultimate excretion occurs in urine. Drugs that attain high concentrations in bile are erythromycin, ampicillin, rifampin, tetracycline, oral contraceptives.

Certain drugs are excreted directly in colon, e.g. anthracene purgatives, heavy metals.

3. Exhaled air Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. Saliva and sweat These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

5. Milk The excretion of a drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better. Milk has a lower pH (7.0) than plasma, basic drugs are somewhat more concentrated in it. However, the total amount of drug reaching the infant through breastfeeding is generally small. As such, majority of drugs can be given to lactating mothers without ill effects on the infant. Nevertheless, it is advisable to administer any drug to a lactating women only when essential.

RENAL EXCRETION

The kidney is responsible for excreting all water-soluble substances. The amount of unaltered drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion (Fig. 2.12).

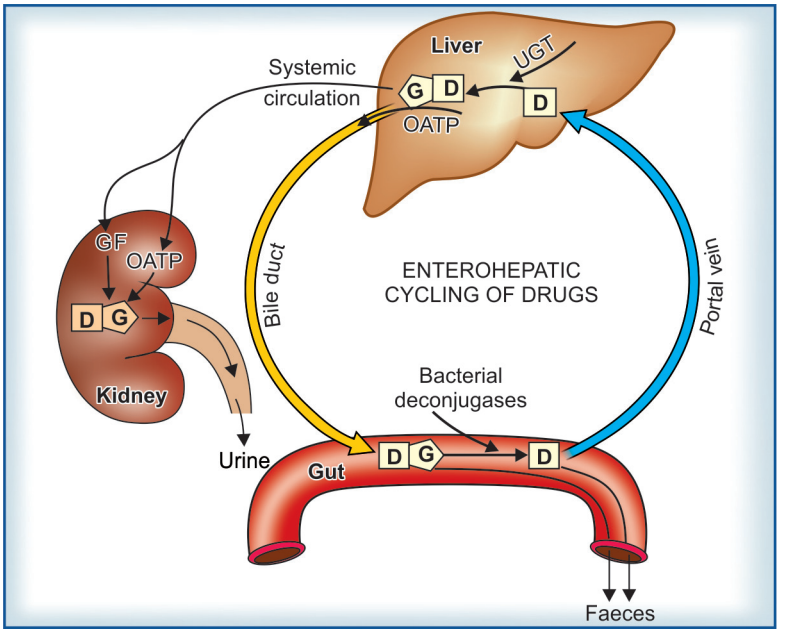

Fig. 2.11: Enterohepatic cycling of drugs
In the liver many drugs (D), including steroids, are conjugated by the enzyme UDP-glucuronosyl transferases (UGTs) to form drug-glucuronide (DG). Part of the DG enters systemic circulation and is excreted into urine by the kidney through both glomerular filtration (GF) as well as active tubular secretion involving renal organic-anion transporting peptide (OATP).

Another part of DG is actively secreted into bile by the hepatic OATP. On reaching the gut lumen via bile, a major part of DG is deconjugated by bacterial hydrolytic enzymes (deconjugates) while the remaining is excreted into faeces. The released D is reabsorbed from the gut to again reach the liver through portal circulation and complete the enterohepatic cycle.

$$\text{Net renal excretion} = (\text{glomerular filtration} + \text{tubular secretion}) - \text{tubular reabsorption}$$

Glomerular filtration Glomerular capillaries have pores larger than usual; all nonprotein bound drug (whether-lipid soluble or insoluble) presented to the glomerulus is filtered. Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow. Glomerular filtration rate (g.f.r.), normally ~ 120 mL/min, declines progressively after the age of 50 and is low in renal failure.

Tubular reabsorption This depends on lipid solubility and ionization of the drug at the existing urinary pH. Lipid-soluble drugs filtered at the glomerulus back diffuse passively in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so. Thus, rate of excretion of such drugs, e.g. aminoglycoside antibiotics, quaternary ammonium compounds parallels g.f.r. (or creatinine clearance). Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized—

- Weak bases ionize more and are less reabsorbed in acidic urine.
- Weak acids ionize more and are less reabsorbed in alkaline urine.

Tubular secretion Tubular secretion is the active transfer of organic acids and bases

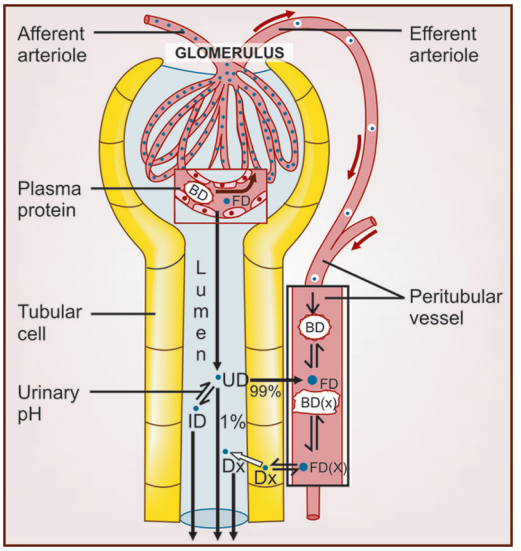

Fig. 2.12: Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs
FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug, Dx—highly secreted organic acid (or base) drug

by two separate classes of nonspecific transporters (OATP and OCT) which operate in the proximal tubules. In addition, efflux transporters P-gp and MRP2 are located in luminal membrane of proximal tubular cells. If renal clearance of a drug is greater than 120 mL/min or g.f.r., additional tubular secretion can be assumed to be occurring.

Active transport of the drug across the tubules reduces the concentration of its free form in the tubular vessels and promotes dissociation of protein bound drug, which again becomes available for secretion (Fig. 2.12). Thus, tubular secretion is very important for renal excretion of highly plasma protein bound drugs which are not removed by glomerular filtration.

(a) *Organic acid transport (by OATP)* It operates for penicillin, probenecid, uric acid, salicylates, sulfinpyrazone, nitrofurantoin, methotrexate, drug glucuronides, etc.

(b) *Organic base transport* (through OCT) This operates for thiazides, quinine, procainamide, choline, cimetidine, amiloride, etc.

Inherently both transport processes are bidirectional, i.e. they can transport their substrate from blood to tubular fluid and vice versa. However, for drugs and their metabolites (which are exogenous substances) secretion into the tubular lumen predominates, while an endogenous substrate like uric acid is predominantly reabsorbed.

Drugs utilizing the same active transport compete with each other. Probenecid is an organic acid which has high affinity for the tubular OATP. It blocks the active transport of both penicillin and uric acid, but whereas the net excretion of the former is decreased, that of the latter is increased. This is because penicillin is primarily secreted while uric acid is primarily reabsorbed. Many drug interactions occur due to competition for tubular secretion, e.g.

(i) Aspirin blocks uricosuric action of probenecid and sulfinpyrazone and decreases tubular secretion of methotrexate.

(ii) Probenecid decreases the concentration of nitrofurantoin in urine, increases the duration of action of penicillin/ampicillin and impairs secretion of methotrexate.

(iii) Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier P-gp.

Tubular transport mechanisms are not well developed at birth. As a result, duration of action of many drugs, e.g. penicillin, cephalosporins, aspirin is longer in neonates. These systems mature during infancy. Renal function again progressively declines after the age of 50 years. The renal clearance of many drugs is substantially lower in the elderly above 75 years of age.

KINETICS OF DRUG ELIMINATION

The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs. There are three fundamental pharmacokinetic parameters, viz. bioavailability (F), volume of distribution (V) and clearance (CL) which must be understood. The first two have already been considered.

Drug elimination is the sum total of metabolic inactivation and excretion. As depicted in Fig. 2.1, drug is eliminated only from the central compartment (blood) which is in equilibrium with peripheral compartments including the site of action. Depending upon the ability of the body to eliminate a drug, a certain fraction of the central compartment may be considered to be totally 'cleared' of that drug in a given period of time to account for elimination over that period.

Clearance (CL) The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time (analogy creatinine clearance, Fig. 2.13). It can be calculated as

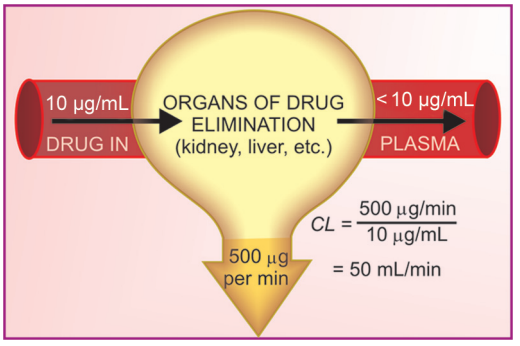

Fig. 2.13: Illustration of the concept of drug clearance. A fraction of the drug molecules present in plasma are removed on each passage through the organs of elimination. In the case shown, it requires 50 mL of plasma to account for the amount of drug being eliminated every minute: clearance is 50 mL/min

$$CL = \text{Rate of elimination}/C \quad ...(4)$$

where C is the plasma concentration.

For majority of drugs the processes involved in elimination are not saturated over the clinically obtained concentrations, they follow:

First order (exponential) kinetics The rate of elimination is directly proportional to drug concentration, CL remains constant; or a constant *fraction* of the drug present in the body is eliminated in unit time. This is the case with majority of drugs.

Few drugs, however, saturate eliminating mechanisms and are handled by—

Zero order (linear) kinetics The rate of elimination remains constant irrespective of drug concentration, CL decreases with increase in concentration; or a constant amount of the drug is eliminated in unit time, e.g. ethyl alcohol.

The elimination of some drugs approaches saturation over the therapeutic range, kinetics changes from first order to zero order at higher doses. As a result, plasma concentration increases disproportionately with increase in dose (*see* Fig. 2.15) as occurs in the case of phenytoin, tolbutamide, theophylline, warfarin.

Plasma half-life The plasma half-life ($t_{½}$) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

Taking the simplest case of a drug which has rapid one compartment distribution, first order elimination, and is given i.v., a semilog plasma concentration-time plot as shown in Fig. 2.14 is obtained. The plot has two slopes:
(i) Initial rapidly declining (α) phase—due to distribution.
(ii) Later less declined (β) phase—due to elimination.
At least two half-lives (distribution $t_{½}$ and elimination $t_{½}$) can be calculated from the

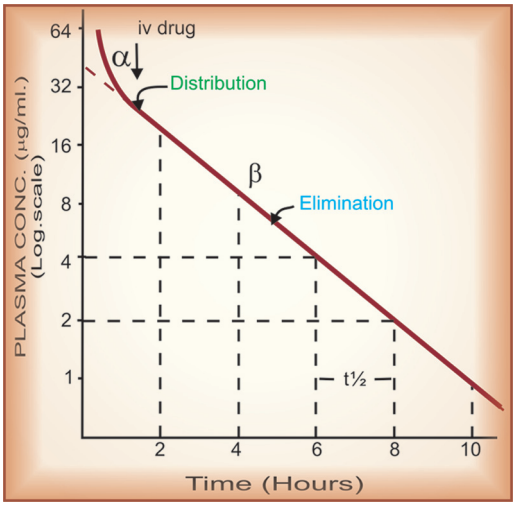

Fig. 2.14: Semilog plasma concentration-time plot of a drug eliminated by first order kinetics after intravenous injection

two slopes. The elimination half-life derived from the β slope is simply called the 'half-life' of the drug. Since first order kinetics is an exponential process, the elimination t½ is

$$t½ = \frac{\ln 2}{k} \qquad ...(5)$$

Where ln2 is the natural logarithm of 2 (or 0.693) and *k* is the *elimination rate constant* of the drug, i.e. the fraction of the total amount of drug in the body which is removed per unit time. For example, if 2 g of the drug is present in the body and 0.1 g is eliminated every hour, then $k = 0.1/2 = 0.05$. It is calculated as:

$$k = \frac{CL}{V} \qquad ...(6)$$

therefore, $$t½ = 0.693 \times \frac{V}{CL} \qquad ...(7)$$

As such, half-life is a derived parameter from two variables V and CL, both of which may change independently. It, therefore, is not an exact index of drug elimination. Nevertheless, it is a simple and useful guide to the sojourn of the drug in the body, i.e. after

1 t½ – 50% drug is eliminated.
2 t½ – 75% (50 + 25) drug is eliminated.
3 t½ – 87.5% (50 + 25 + 12.5) drug is eliminated.
4 t½ – 93.75% (50 + 25 + 12.5 + 6.25) drug is eliminated.

Thus, nearly complete drug elimination occurs in 4–5 half-lives.

For drugs eliminated by—

First order kinetics—t½ remains constant because *V* and *CL* do not change with dose.

Zero order kinetics—t½ gets prolonged with increase in dose because *CL* progressively decreases as dose is increased.

Half-life of some representative drugs			
Aspirin	4 hr	Digoxin	40 hr
Penicillin-G	30 min	Metronidazole	8 hr
Doxycycline	20 hr	Phenobarbitone	90 hr

Repeated drug administration

When a drug is repeated at relatively short intervals, it accumulates in the body until elimination balances input and a steady-state plasma concentration (C*pss*) is attained—

$$Cpss = \frac{\text{dose rate}}{CL} \qquad ...(8)$$

From this equation it is implied that doubling the dose rate would double the average C*pss* and so on. Further, if the therapeutic plasma concentration of the drug has been worked out and its *CL* is known, the dose rate needed to achieve the target C*pss* can be determined—

$$\text{dose rate} = \text{target } Cpss \times CL \qquad ...(9)$$

After oral administration, often only a fraction (F) of the dose reaches systemic circulation in the active form. In such a case—

$$\text{dose rate} = \frac{\text{target } Cpss \times CL}{F} \qquad ...(10)$$

The dose rate-Cpss relationship is linear only in case of drugs eliminated by first order kinetics. For drugs (e.g. phenytoin) which follow Michaelis Menten kinetics, elimination changes from first order to zero

order kinetics over the therapeutic range. Increase in their dose beyond saturation levels causes an increase in Cpss which is out of proportion to the change in dose rate (Fig. 2.15). In their case:

$$\text{Rate of drug elimination} = \frac{(V_{max})(C)}{K_m + C} \quad ...(11)$$

where C is the plasma concentration of the drug, Vmax is the maximum rate of drug elimination, and Km is the plasma concentration at which elimination rate is half maximal.

Plateau principle

When a constant dose of a drug is repeated before the expiry of 4 t½, it would achieve higher peak concentration, because some remnant of the previous dose will be present in the body. This continues with every dose until progressively increasing rate of elimination (which increases with increase in concentration) balances the amount administered over the dose interval. Subsequently, plasma concentration plateaus and fluctuates about an average steady-state level. This is known as the plateau principle of drug accumulation. Steady state is reached in 4–5 half-lives unless dose interval is very much longer than t½ (Fig. 2.16).

The amplitude of fluctuations in plasma concentration at steady state depends on the dose interval relative to t½, i.e. the difference between the maximum and minimum levels is less if smaller doses are repeated more frequently (dose rate remaining constant). Dosage intervals are generally a compromise between what amplitude of fluctuations is clinically acceptable (loss of efficacy at troughs and side effects at peaks) and what frequency of dosing is convenient. However, if the dose rate is changed, a new average Cpss is attained over the next 4–5 half-lives. When the drug is administered orally (absorption takes some time), average Cpss is approximately 1/3rd of the way between the minimal and maximal levels in a dose interval. Knowledge of half life of a drug in very helpful in devising its dosage regimen.

Target level strategy For drugs whose effects are not easily quantifiable and safety margin is not big, e.g. anticonvulsants, antidepressants, lithium, some antimicrobials, etc. or those given to prevent an event, it is best to aim at achieving a certain plasma concentration which has been defined to be in the therapeutic range;

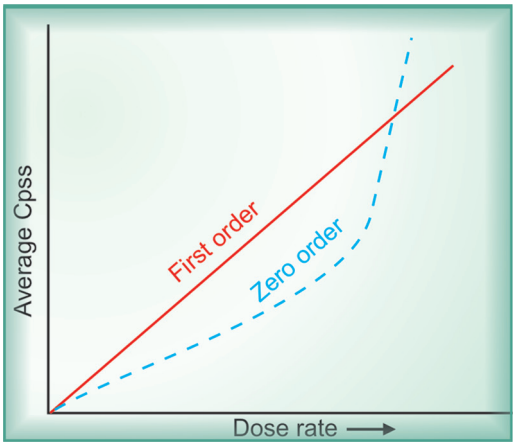

Fig. 2.15: Relationship between dose rate and average steady-state plasma concentration of drugs eliminated by first order and Michaelis Menten (zero order) kinetics

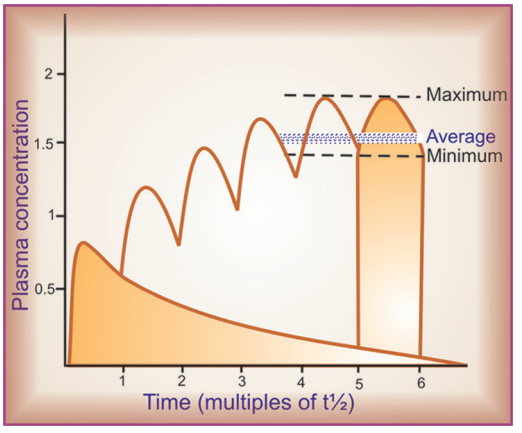

Fig. 2.16: Plateau principle of drug accumulation on repeated oral dosing
Note. The area of the two shaded portions is equal.

such data are now available for most drugs of this type.

Drugs with short t½ (up to 2–3 hr) administered at conventional intervals (6–12 hr) achieve the target levels only intermittently and fluctuations in plasma concentration are marked. In case of many drugs (penicillin, ampicillin, chloramphenicol, erythromycin, propranolol) this, however, is therapeutically acceptable.

For drugs with longer t½ a dose that is sufficient to attain the target concentration after a single administration, if repeated will accumulate according to plateau principle and produce toxicity later on. On the other hand, if the dosing is such as to attain target level at steady state, the therapeutic effect will be delayed by about 4 half-lives (this may be clinically unacceptable). Such drugs are often administered by initial loading and subsequent maintenance doses.

Loading dose This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly. It may be calculated as—

$$\text{Loading dose} = \frac{\text{target } Cp \times V}{F} \quad \ldots(12)$$

Thus, loading dose is governed only by V and not by CL or t½.

Maintenance dose This dose is one that is to be repeated at specified intervals after the attainment of target Cpss so as to maintain the same by balancing elimination. The maintenance dose rate is computed by equation (10) and is governed by CL (or t½) of the drug. If facilities for measurement of drug concentration are available, attainment of target level in a patient can be verified subsequently and dose rate adjusted if required.

Such two phase dosing provides rapid therapeutic effect with long-term safety. This is frequently applied to digoxin, chloroquine, doxycycline, etc. However, if there is no urgency, maintenance doses can be given from the beginning.

PROLONGATION OF DRUG ACTION

It is sometimes advantageous to modify a drug in such a way that it acts for a longer period. By doing so:
(i) Frequency of administration is reduced, which is more convenient.
(ii) Improved patient compliance—a single morning dose is less likely to be forgotten/omitted than a 6 or 8 hourly regimen.
(iii) Large fluctuations in plasma concentration are avoided—side effects related to high peak plasma level soon after a dose would be minimized (e.g. nifedipine); better round-the-clock control of blood sugar level, etc.
(iv) Drug effect could be maintained overnight without disturbing sleep, e.g. antiasthmatics, anticonvulsants, etc.

However, all drugs do not need to be made long acting, e.g. those used for brief therapeutic effect (sleep inducing hypnotic, headache remedy) or those with inherently long duration of action (digoxin, amlodipine, doxycycline, omeprazole). Drugs with t½ < 4 hr are suitable for controlled release formulations, while there is no need of such formulations for drugs with t½ >12 hr. Methods utilized for prolonging drug action are summarized below. Some of these have already been described.

1. By prolonging absorption from site of administration

(a) *Oral* Sustained release tablets, spansule capsules, etc.; drug particles are coated with resins, plastic materials or other substances which temporally disperse release of the active ingredient in the g.i.t. The controlled release tablet/capsule preparation utilizes a semipermeable membrane to control the release of drug from the dosage form. Such preparations prolong the action by 4 to 6

hours and no more because in that time drug particles reach the colon.

(b) *Parenteral* The s.c. and i.m. injection of drug in insoluble form (benzathine penicillin, lente insulin) or as oily solution (depot progestins); pellet implantation, sialistic and biodegradable implants can provide for its absorption over a couple of days to several months or even years. Inclusion of a vasoconstrictor with the drug also delays absorption (adrenaline with local anaesthetics).

(c) *Transdermal drug delivery systems* The drug impregnated in adhesive patches, strips or as ointment is applied on skin for prolonged absorption.

2. By increasing plasma protein binding Drug congeners have been prepared which are highly bound to plasma protein and are slowly released in the free active form, e.g. sulfadoxine.

3. By retarding rate of metabolism Small chemical modification can markedly affect the rate of metabolism without affecting the biological action, e.g. addition of ethinyl group to estradiol makes it longer acting and suitable for use as oral contraceptive. Inhibition of specific enzyme by one drug can prolong the action of another drug, e.g. allopurinol inhibits degradation of 6-mercaptopurine; ritonavir boosts the action of atazanavir and lopinavir; cilastatin protects imipenem from degradation in kidney.

4. By retarding renal excretion The tubular secretion of drug being an active process, can be suppressed by a competing substance, e.g. probenecid prolongs duration of action of penicillin and ampicillin.