PART A

Drug Discovery and General Pharmacology

1 SECTION

Drug Discovery and Man

2 SECTION

General Pharmacology

1 SECTION

Drug Discovery and Man

1. Drug Discovery and Man

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Drug Discovery and Man

1240 : Pharmacy officially separated from medicine.

1400 : Ortolff of Wurzburg wrote one of the first drug manuals '*Artzneibuch*'; but published by Zainer in Augsburg in 1477.

1525 :
- F de Oviedo, Viceroy of Mexico published his '*Summarie*' in Toledo, the first description of medicinal plants.
- Rycherde Bankes published the first English herbal text in London.

1546 : Valerius Cordus compiled the best officially recognized book of drug preparations a 'pharmacopoeia'—'*Dispensatorium Pharmacopolarum*'. It went into 35 editions and 5 translations.

1551 : William Turner issued '*A New Herbal*' in three volumes (1551–1568) published in London.

1563 : Garcia de Huerta published in Goa his '*Cologuias dos simples*', the first effort by an European to describe the rich indigenous plant drugs of India.

1580 : The term 'Pharmacopoeia' was first used officially from Greek words—*Pharmacon* (drug) and *Poiein* (make).

1618 : Royal College of Physicians issued '*Pharmacopoeia Londinensis*'.

1633 : Augustinian monk Calancha issued the first written statement of the use of cinchona for fevers.

1662 : Johann Daniel Major of Kiel first gave IV injection to humans.

1772 : Priestley discovered nitrous oxide.

1785 : William Withering published his 'Account of the foxglove and some of its medicinal uses' (first account of digoxin use).

1794 : Beddoes introduced oxygen therapy in England.

1800 : Discovery of analgesic properties of nitrous oxide by Davy who named it 'laughing gas'.

1805 : Serturner Friedrich isolated morphine from opium.

1820 :
- First United States pharmacopoeia was published.
- Pelletier and Caventou isolated quinine from cinchona.

1828 : Posselt and Reiman first isolated nicotine from the leaves of tobacco, Nicotiana tobacum.

1831 : Mein isolated atropine in pure form.

1839 : Tincture of iodine first used as an antiseptic by a French surgeon.

1844 : Horace Wells introduced nitrous oxide inhalation to produce anaesthesia.

1846 :
- First successful demonstration of ether anaesthesia by WTG Morton at Massachusetts General Hospital, Boston (Birth of General Anaesthesia).

- Sobrero first synthesized nitroglycerin.

1847 :
- Constantin Hering developed sublingual dosage form for nitroglycerin.
- James Simpson introduced chloroform anaesthesia.

1872 :
- Antisalivary effects of atropine described by RPH Heidenhain.
- Salicylic acid synthesized from phenol.

1877 : Pasteur and Joubart first recognised the clinical potentialities of microorganisms as therapeutic agents.

1879 : William Murrell established use of sublingual nitroglycerine for relief of acute anginal attack and as a prophylactic to be taken prior to exertion.

1884 : Sigmund Freud and Karl Koller demonstrated local anaesthetic properties of cocaine on the cornea; first mandibular block given by W Stewart Halsted and Hall, New York.

1895 : Oliver and Schafer first showed the effects of suprarenal extracts, active principle of which was named as 'epinephrine' by Abel in 1899.

1898 :
- Teigerstedt and Bergman discovered renin.
- Lewandowsky noted the similarity between the effects of injection of extracts on the adrenal gland and stimulation of sympathetic nerves; confirmed in 1901 by Langley.

1899 : Heinrich Dreser named acetyl salicylic acid 'aspirin' and introduced it to clinical use.

1902 : Heinrich Braun added adrenaline to cocaine solution to prolong its effect and retard its absorption.

1903 : Emil Fischer and Von Mering of Munich synthesized barbitone, the first barbiturate.

1904 : Procaine synthesized by Alfred Einhorn.

1905 : Langley suggested that effector cells have excitatory and inhibitory 'receptive substances'.

1906 :
- Dale discovered alpha blockers (ergot alkaloids).
- The first federal law designed to regulate drug products in USA (Food and Drugs Act).

1910 : P Ehrlich and S Hata discovered arsphenamine for syphilis.

1912 :
- Vedder showed that emetine killed amoebae *in vitro*.
- Phenobarbitone introduced in therapeutics.

1914 : Dale introduced the term 'parasympathomimetic'.

1916 : Jay Mclean, a medical student, discovered heparin; named so by Howell in 1922.

1921 :
- Otto Loewi established the first real proof of the chemical mediation of nerve impulses by the peripheral release of specific chemical agents.
- Frederick Banting and a medical student Charles Best isolated insulin.

1928 : Sir Alexander Fleming discovered penicillin.

1930 : R Kurzrok and CC Lieb observed that strips of human uterus relax or contract when exposed to human semen (birth of 'prostaglandins', so named by Euler).

1931 : Sen and Bose described the application of Rauwolfia in psychosis and hypertension.

1935 : JS Lundy demonstrated use of thiopental, rapidly acting barbiturate.

1938 : Merritt and Putnam discovered anticonvulsant activity of phenytoin.

1939 : Schaumann and Eisleb synthesized pethidine.

1941 : Cowdry and Ruangsiri first demonstrated favourable effect of glucosulfone (derivative of dapsone) in leprosy.

1942 : Griffith and Johnson used curare in anaesthesia.

1943 : Albert Hoffman synthesized LSD.

1944 : Waksman, Schatz and Bugie discovered streptomycin.

1945 : Chorine discovered INH.

1947 : Burkholder discovered chloramphenicol.

1948 :
- RP Ahlquist classified adrenoceptors into alpha (α) and beta (β).
- MM Rapport and colleagues isolated serotonin (5-HT).
- Brotzu discovered cephalosporins.
- Tetracyclines introduced in therapeutics.

1949 :
- JFJ Cade first reported the use of lithium in mania.
- Hexamethonium described by Paton and Zaimis, short-acting muscle relaxants described by Daniel Bovet.

1950 : GABA was identified as an unique chemical constituent of brain.

1951 :
- First volume of '*Pharmacopoeia Internationalis*' published by WHO.
- Halothane synthesized by Sucking of Manchester.

1952 :
- Laborit recognised the unique effect of chlorpromazine and J Delay and J Deniker used it in psychiatric patients.
- McGuire discovered erythromycin.

1954 : Dale coined the terms 'cholinoceptive' and 'adrenoceptive'.

1956 :
- Bristow et al introduced diloxanide furoate.
- Halothane introduced in clinical practice by Michael Johnstone.

1957 :
- LH Sternbach developed chlordiazepoxide, which was later introduced in therapy in 1961.
- Rock, Pincus and Garcia first demonstrated the inhibition of ovulation by drugs (birth of oral contraceptives).

1958 :
- Powell and Slater discovered the first beta blocker dichloroisoproterenol.
- PA Janssen discovered antipsychotic properties of haloperidol.
- R Kuhn recognised antidepressant effects of imipramine.

1961 : Thomas and coworkers discovered ethambutol.

1965 :
- Stoughton first conceived the concept of percutaneous drug absorption.
- Dole and Nyswander introduced methadone as treatment for opioid dependence.

1966 :
- Ketamine used clinically by Corssen and Domino, USA.
- Enflurane used by Virtue of Denver.

1970 : Levodopa introduced in therapeutics.

1971 : Isoflurane first used in anaesthesia.

1972 : JW Black and others discovered H_2 blockers.

1973 : Amantadine approved for use.

1974 : Carbamazepine approved as an antiepileptic.

1975 : Dr. William Campbell discovered ivermectin.

1978 :
- Neu and Fu discovered clavulanic acid.
- Bromocriptine approved for use.

1987 : Zidovudine introduced as the first anti-HIV drug for clinical use.

1988 : Pergolide approved for use.

1989 : Selegiline approved for parkinsonism.

1990 : Two isoforms of cyclo-oxygenase (COX) suggested.

1991 : Didanosine approved for HIV infection.

1992 :
- COX-2 cloned from humans.
- Zalcitabine approved for use.

1993 : LAAM approved for treatment of opioid addiction.

1994 : Stavudine introduced for HIV infection.

1995 : First protease inhibitor saquinavir introduced; lamivudine also approved.

1996 : First non-nucleoside reverse transcriptase inhibitor nevirapine introduced, ritonavir and indinavir also approved.

1997 :
- Pramipexole and ropinirole approved for parkinsonism.
- Nelfinavir and delavirdine introduced.

1998 :
- Tolcapone, the first COMT inhibitor introduced.
- Abacavir and efavirenz launched for HIV infection.

1999 : Entacapone introduced for parkinsonism.

2000 : Lopinavir approved in combination with ritonavir as a fixed dose combination for HIV infection.

2001 : First nucleotide reverse transcriptase inhibitor approved (Tenofovir).

2003 : First fusion inhibitor enfuvirtide launched; emtricitabine, atazanavir and fosamprenavir approved.

2004 : Insulin glulisine, nitazoxanide, acamprosate approved.

2005 : Abatacept introduced for rheumatoid arthritis.

2006 : First DPP-4 inhibitor sitagliptin approved for type 2 DM; Darunavir approved for HIV infection.

2007 : First chemokine CCR-5 receptor blocker approved (maraviroc); first integrase inhibitor approved (raltegravir).

2008 : Rufinamide launched for Lennox-Gastaut Syndrome.

2009 : Milnacipran approved for fibromyalgia; Febuxostat introduced for gout.

2010 : Ceftaroline, a 5th generation cephalosporin approved.

2011 :
- Ruloxitinib approved for myelofibrosis.
- Abiraterone, first androgen synthesis inhibitor approved for prostate cancer.

2012 : Ivacaftor approved for cystic fibrosis.

2013 :
- First in class dual PPAR α, γ agonist, saroglitazar approved in India by DCGI.
- First SGLT-2 inhibitor canagliflozin approved.

2014 : PCSK 9 inhibitor, evolocumab approved for hyperlipidaemia.

2015 : Rolapitant, NK1 receptor antagonist approved for chemotherapy-induced emesis.

2016 : First antisense therapy, eteplirsen, approved for use in Duchenne muscular atrophy.

2017 : Letermovir approved for prevention of CMV infection in transplant patients.

2018 :
- First antipox viral, tecovirimat, approved for smallpox and monkey pox.
- Lusutrombopag approved for thrombocytopenia in chronic liver disease.

2019 :
- Erdafitinib, first targeted therapy for breast cancer approved.
- First immunotherapy for breast cancer (Atezolizumab + Nab-paclitaxel) approved for triple negative patients.
- First antibody-drug conjugate, polatuzumab vedotin-piiq approved for large B cell lymphoma.

2020 :
- Teprotumumab-trbw approved for thyroid eye disease.

- Eptinezumab-jjmr approved for prophylaxis and rimegepant for treatment of migraine.
- Ozanimod approved for relapsing multiple sclerosis.
- ICMR approved prophylactic hydroxychloroquine therapy for COVID-19.
- Remdesivir and favipiravir approved for COVID-19.

❍❍❍

FIND OUT

1. Who coined the term “beta-lactamase?
2. Who is known as the ‘Father of modern TB control’?
3. Who first used methadone to treat opioid dependence in 1965?
4. Who discovered emtricitabine for HIV infection?
5. Which scientist first used the term ‘antibiotic’?

2 SECTION

General Pharmacology

2. Routes of Administration and Dosage Forms

3. Clinical Pharmacokinetics

4. Pharmacodynamics

5. Chronopharmacology

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Routes of Administration and Dosage Forms

LEARNING OBJECTIVES

- Merits and demerits of various routes of administration of drugs
- Dosage forms available for drug delivery
- Instructions to patients regarding the use of various dosage forms

ROUTES OF ADMINISTRATION OF DRUGS

(1) **Enteral (gastrointestinal):** Oral, sublingual, buccal, translingual, rectal, newer drug delivery systems.

(2) **Parenteral:** Injections, pulmonary (inhalation), nasal, transdermal, topical, endotracheal, newer drug delivery systems.

Dosage Forms (DF)

Definition: They are the products designed to administer drugs to the patients by various routes for diagnostic, prophylactic or therapeutic purposes.

Advantages of DF

(*a*) Protection of the drug from moisture or influence of atmospheric oxygen, *e.g.,* coated tablets, sealed ampoules.

Classification

(i) Solid DF (> 60%): These include the caplets, capsules, granules, powders, tablets and transdermal patches. Powders are least popular for oral use, popular for topical use and very popular for parenteral use.

(ii) Liquid DF (30%): These include solutions (true solutions, syrups, elixirs, drops) and dispersions (suspensions, lotions, liniments, emulsions). Suspensions and emulsions can be given by any route except intravenous. Lotions and liniments are always used topically.

(iii) Semi-solid DF (8–10%): These include creams, gels, ointments and suppositories.

(iv) Gaseous DF (<2%): These include oral inhalers, aerosols and sprays. They are expensive.

(*b*) Protection of the drug from destruction by gastric acid on oral administration, *e.g.,* enteric coated tablets.

(*c*) Masking the bad taste and foul odour of drugs, *e.g.,* capsules, sugar-coated tablets, flavoured syrups.

(*d*) Preparation of liquid products of substances which are soluble, insoluble or unstable in desired vehicle, *e.g.,* solutions, suspensions, emulsions.

(*e*) Provision of controlled-release mechanisms for a prolonged period of time, *e.g.,* extended-release preparations, osmotic delivery systems, transdermal patches/discs.

(*f*) Preparation of drugs for quick action in emergencies, *e.g.,* sublingual tablets, buccal tablets, dispersible tablets, injections.

(*g*) Provision of optimal drug action on skin and mucous membranes when used topically.

(h) Provision of systemic action on topical administration, *e.g.,* nasal delivery systems, transdermal ointment.

(*i*) Provision of drug administration into body orifices, *e.g.,* rectal suppositories, vaginal pessaries.

(*j*) Provision of targeted drug delivery to body tissues and organs, *e.g.,* injections, liposomal drug delivery, ocuserts, progestaserts.

(*k*) Provision of drug action directly into lungs, *e.g.,* aerosols, gases.

(*l*) Provision of self-regulatory delivery system to patients, *e.g.,* patient-controlled analgesia pump.

I. ENTERAL ROUTE

A. Oral Route (Ingestion)

This is the oldest and the commonest route of administration of drugs.

Merits:

(1) This route is safer than the parenteral route.

(2) It is convenient, painless and acceptable to the patients.

(3) Self-medication is possible and assistance is not required.

(4) It is generally cheaper than other routes. (Newer antibiotic oral preparations are often very expensive.)

Demerits:

(1) As onset of action is slow, the route cannot be employed in emergencies.

(2) Oral route cannot be used in the case of:

(*i*) Drugs destroyed extensively in liver during first pass, *e.g.,* lignocaine.

(ii) Polar drugs as they are not absorbed orally, *e.g.,* aminoglycosides.

(*iii*) Unconscious, uncooperative bedridden patients and those with severe vomiting.

(*iv*) Drugs destroyed by gastric enzymes, *e.g.,* insulin, adrenaline.

(3) Food may interfere with absorption (can decrease or delay) of some drugs.

Dosage Forms

(1) **Solid DF:** Tablets, capsules, pills, powders, lozenges.

(2) **Liquid DF:** Simple mixtures (true solutions), suspensions, emulsions, elixirs.

SOLID DF

A. Tablets: These are the DF containing granulated or powdered drugs that are compressed or moulded into various shapes (round, discoid, triangular, oval, heart-shaped, etc.). In addition to the active drug, compressed tablets contain a number of inert substances known as additives or excipients which include:

(*i*) ***Diluents or fillers:*** These are added to add the necessary bulk if the amount of active ingredient is small, *e.g.,* dicalcium phosphate, calcium phosphate, lactose.

(*ii*) ***Lubricants:*** These are added to prevent adhesion of the tablet material to the surface of the dies and punches and to reduce interparticle friction, *e.g.,* talc, magnesium stearate.

(*iii*) ***Disintegrents:*** These are added to facilitate the tablet breakup or disintegration after ingestion, *e.g.*, corn starch, potato starch.

(*iv*) ***Binders or adhesives:*** These are added to bind the components together and to maintain the integrity of the final tablet, *e.g.*, gelatin, sucrose, starch.

(*v*) ***Colouring agents or colourants:*** These are added for aesthetic reasons and for identification. Only approved colours are used, *e.g.*, allure red, tartrazine, quinoline yellow, brilliant blue.

(*vi*) ***Flavouring agents or flavourants:*** These are added to impart sweetness, pleasant flavour and odour, *e.g.*, aspartame, anise oil, cinnamon oil.

Some excipients used in the formulation of DF are known to form a complex with some drugs, rendering a portion or all of the administered dose unavailable for absorption.

Excipients		Drugs interfered with
1.	Dicalcium phosphate	Tetracycline
2.	Sodium carboxy-methylcellulose	Amphetamine
3.	Polyethylene glycol	Phenobarbitone

Tablet modifications: Tablets are modified into various types. Common modifications are as under:

(*i*) ***Multiple compressed tablets:*** These are prepared by subjecting the fill material to more than a single compression. The result may be a multilayered tablet or a tablet- within-a- tablet, the inner tablet being the core and the outer portion being the shell (Fig. 2.1).

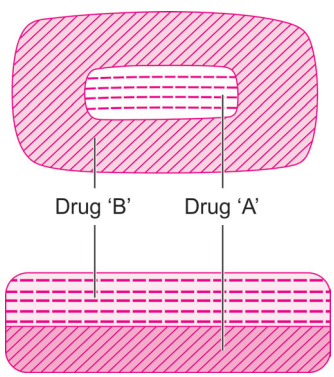

Fig. 2.1 Multiple compressed tablets

(*ii*) ***Chewable tablets:*** These are pleasant tasting tablets formulated to disintegrate smoothly in the mouth. They are especially useful for administration of tablets of large size to children and adults who have difficulty swallowing solid DF, *e.g.,* albendazole, simethicone/ antacid tablets.

(iii) ***Coated tablets:*** These are compressed tablets covered by various coatings. The main reasons to coat a tablet are:

(*a*) To facilitate absorption

(*b*) To prevent gastric irritation

(c) To prevent alteration of drug in the stomach

(*d*) To have prolonged duration of action

(*e*) To mask the bitter taste of the drug.

Coatings on the tablets:

(*a*) ***Film coating:*** This involves the deposition of a thin, but uniform film onto the surface of the substrate. These coatings can be applied to pharmaceutical products often to modify drug release. Two types of modified release coated DF are available: delayed release and extended release DF

(*i*) ***Enteric coatings:*** These are film coatings used to prepare delayed release DF They remain intact in the stomach but dissolve and release the contents of the DF once they reach the small intestine. The purpose of an enteric coating is to delay the release of drugs that are inactivated by the stomach contents (*e.g.,* erythromycin) or may cause nausea or bleeding by irritating the gastric mucosa (*e.g.,* aspirin, steroids). The enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid, carboxy-methyl ethyl cellulose, etc.

(*ii*) ***Sustained-release coatings:*** These are film coatings used to prepare extended release DF to extend drug release over a period of time. The film coatings are first applied to drug crystals or compacted into tablets. The materials used to produce sustained-release coatings are bees-wax, shellac, zein,

ethylcellulose, etc. One must be aware that, if the entire dose is released quickly (dose-dumping), toxicity may result.

(*b*) ***Sugar coating:*** This is a thin water-soluble coating used to mask the taste and odour of the drug. Liquid glucose or sucrose are used.

(c) ***Gelatin coating:*** This coating allows the product to be about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates swallowing and is more tamper-evident.

B. Capsules: These are small, soluble containers made of tasteless gelatin. They may be hard (hard gelatin capsules) or soft (soft elastic capsules) depending on the amount of glycerin in gelatin. They are filled with powders, semi-solids or liquids that are non-solvent in gelatin. Sizes range from small (5) to big (000). Unpalatable drugs are usually dispensed in capsules. Capsules, like tablets, can be enteric-coated and sustained-release types.

Multi-tablet capsule system: Small spheroid-shaped compressed mini-tablets 3–4 mm in diameter are prepared to have varying release characteristics. These are then incorporated in a capsule (8–10 mini-tablets in each). Some of these mini-tablets are uncoated for immediate release and others are coated for extended drug release.

C. Powders: These are solid DF which contain one (simple powder) or more (compound powder) ingredients mixed with each other in a dry and finely divided state. The powders are usually dispensed in sachets.

D. Lozenges (troches or pastilles): These are discoid-shaped solid DF containing the drug in a suitably flavoured base like hard sugar candy. They are placed in the mouth, where they slowly dissolve, liberating the active ingredient.

LIQUID DF

(a) **Mixtures:** These are liquid medicants containing dissolved, suspended or emulsified substances in a suitable vehicle and is meant for internal use. They are of three types as follows:

(i) ***Simple mixtures:*** They are mixtures containing ingredients that dissolve in the vehicle.

(*ii*) ***Suspensions:*** They are preparations of ingredients insoluble in the vehicle, dispensed in such a way that on agitation (shaking of bottle) uniform distribution of the ingredients occurs.

(*iii*) ***Emulsions:*** These contain two immiscible liquids, one of which is finely divided into small globules and dispensed into the other with the help of emulsifying agents like gum acacia.

(*b*) **Elixirs:** These are sweetened, pleasantly flavoured hydroalcoholic solutions of drugs.

(*c*) **Syrups:** These are solutions of flavouring or medicinal substances in an almost saturated solution of sucrose in water.

(*d*) **Linctuses:** These are viscous, syrupy, mucilaginous liquid preparations used for local action on the mucosa of the throat. Active ingredients after absorption also act at other sites for beneficial effects. They are slowly sipped, *e.g.,* codeine linctus.

(*e*) **Tinctures:** These are alcoholic solutions of active principles of crude drugs either for oral or external use, *e.g.,* Tincture belladonna (internal), Tincture iodine (external).

B. Sublingual Route

Drug is placed under the patient's tongue and allowed to be dissolved through the buccal mucosa without entry into the system. The thin epithelium and rich capillary network under the tongue permit rapid absorption and drug action. The patient is advised not to take water or fluids immediately after the tablet.

Merits:

(1) The absorption of the drug and its onset of action is rapid.

(2) The drug bypasses the hepatic circulation and escapes first pass metabolism.

(3) Termination of the drug effect is possible by spitting out the tablet.

Demerits:
(1) The drug has to be kept in the mouth for a period of time.
(2) Irritation of mouth and ulceration of oral mucosa are common.
(3) Excessive salivation can promote swallowing.

Drugs administered sublingually: Glyceryl trinitrate, isosorbide dinitrate, nifedipine, oxytocin, alphachymotrypsin, buprenorphine, methyl-testosterone, ergotamine, prochlorperazine, pentazocin.

DF: Tablets, capsules (liquid contents poured sublingually).

C. Buccal Route

The drug is applied against the mucosa of the cheek, or under the upper lip above the incisors where it adheres to the gingiva and gradually disappears. Merits/demerits are similar to the sublingual route.
Drugs administered buccally: Glyceryl trinitrate, morphine, fentanyl, nicotine.
DF: Buccal tablets, chewing gum, lozenges.

D. Translingual

The drug is sprayed into the mouth under the tongue for quick effect. The merits and demerits are similar to sublingual and buccal administration.
Drug administered translingually: Nitroglycerine.
DF: Sprays.

E. Rectal

Drugs are administered through the anus into the rectum either as a solution (enema) or as a solid formulation with wax base (suppository). Patients are advised to remove the wrapper of drug formulations before inserting into the anal canal.

Enemata are of two types:
(*a*) **Evacuant enema:** This is used to remove faecal matter and is useful in selective cases of constipation.
(*b*) **Retention enema:** This is used to retain the drug for local or systemic action.

Merits:
(1) The route is useful in infants and young children.
(2) The drug partly bypasses hepatic circulation.
(3) Gastric irritation can be avoided.

Demerits:
(1) The absorption is sometimes variable, incomplete, erratic and unreliable.
(2) Only non-irritant drugs can be given.

Drugs administered rectally: Bisacodyl, diazepam, indomethacin, mesalamine, paracetamol, aspirin, triethylperazine, promethazine, prochlorperazine, oxymorphone, hydromorphone, chlorpromazine.
DF: Rectal suppositories, enemata.

F. Newer Drug Delivery Systems

(1) **Osmotic drug delivery system:** Principle of osmosis is used to produce constant rate of drug release. DF may contain osmotic core containing the active drug which is released through osmotic delivery orifice (osmotic tablets) (Fig. 2.2) or an independent osmotic compartment separating a drug compartment by a diaphragm (osmotic pressure-controlled drug delivery system or gastrointestinal therapeutic system) (Fig. 2.3).
The entire tablet is coated with a semipermeable membrane that allows only water to enter inside. The osmotic compartment swells and pushes the drug out through the delivery orifice.
Drugs administered by osmotic DDS: Prazosin, indomethacin, oxprenolol.

(2) **Mucoadhesive gastric delivery system:** A bioadhesive polymer such as crosslinked polyacrylic acid, when incorporated in a tablet, allows it to adhere to the gastric mucosa or epithelium. Such a system continuously releases a fraction of drug into the intestine over a prolonged period of time, *e.g.,* ferrous sulphate GDS.

Enteral DF that should not be crushed: There are many instances in practice when contents of a solid DF are removed from the DF or a DF is crushed or divided into smaller doses. The reasons

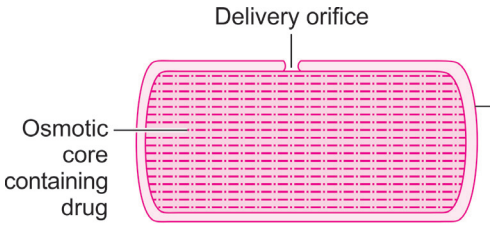

Fig. 2.2 Osmotic tablets

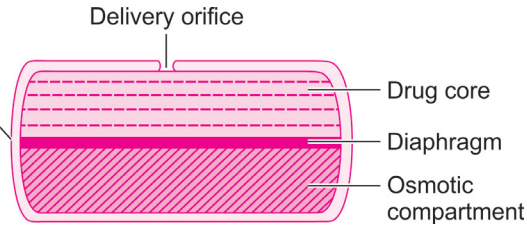

Fig. 2.3 GITS

for crushing the tablet or capsule contents or dividing the DF prior to administration are as follows:

(*i*) For administration to children.
(*ii*) For administration to patients who have difficulty in swallowing the intact DF
(*iii*) In patients with nasogastric tubes.
(*iv*) Oral solution for a particular drug may not be available.
(*v*) Mixing of powdered drug with food or drink may make it more palatable.

DF that should not be crushed or divided fall into the following categories:

(*a*) Enteric coated products
(*b*) Extended release products
(*c*) Sublingual or buccal tablets
(*d*) Film or sugar-coated tablet of unpleasant tasting drug
(*e*) Effervescent tablets
(*f*) Osmotic DDS and mucoadhesive GDS.

II. PARENTERAL ROUTE OF ADMINISTRATION

A. Injections

1. **Intravenous (IV):** In this route, the drug is given directly into the vein. Usually the drug is injected into the cubital vein at the bend of the elbow. Alternately, any other suitable vein could be used.

IV injection can be given as:

(*a*) A bolus, *e.g.,* furosemide, adenosine.
(*b*) Slowly over 5–15 minutes after dilution in 20 to 30 ml of isotonic glucose or saline, *e.g.,* aminophylline.
(*c*) Infusion which is 100 ml or more in volume, *e.g.,* fluids in shock.

Merits:

(1) The onset of action is rapid and is, therefore, valuable in emergencies.
(2) Bioavailability is 100% as all the factors affecting absorption are bypassed.
(3) Large volumes can be infused, *e.g.,* dextrose, normal saline.
(4) Irritant solutions can be given, as the blood vessels are relatively insensitive and if infused slowly, the drug is sufficiently diluted by the blood, *e.g.,* phenytoin.
(5) Doses of drugs can be accurately titrated whenever necessary, *e.g.,* in case of sodium nitroprusside and lignocaine use IV.

Demerits:

(1) Adverse reactions are more likely to occur, as high drug concentrations are achieved rapidly.
(2) Only aqueous solutions can be given.
(3) Self-administration is not possible.
(4) Risk of anaphylaxis is maximum with this route.
(5) Risk of sloughing and necrosis is high, if the drug extravasates.
(6) If air enters the vein accidentally, there are chances of air embolism.

IV infusion: This is IV administration of larger amounts of fluid (usually 1–2 litres). The solution is allowed to flow by gravity from graduated glass bottles or plastic bags through a drip set into the vein. The drug delivery is slow, uniform and controlled.

Uses:

(*i*) To relieve dehydration.
(*ii*) To restore blood volume.
(*iii*) To supply electrolytes, blood, nutrition.
(*iv*) To administer drugs slowly when bolus injection is not desirable or indicated.

Guidelines for IV infusion:

(*a*) If any drug has to be added to the infusion, the mixture should be made immediately before use.

(*b*) If more than one drug is to be added, it is necessary to rule out a drug interaction, *e.g.*, heparin and penicillin should not be mixed.

Demerits: Drugs diluted in IV fluid may lose their potency, *e.g.*,

(*i*) Penicillin loses activity after 16 hrs in normal saline or 5% dextrose.

(*ii*) Ampicillin loses activity after 8 hrs in normal saline and 4 hrs in dextrose.

Drugs administered by IV infusion (large volume parenterals): Amino acids, dextrose, sodium chloride, Ringer's lactate, mannitol.

Diluents for continuous IV infusion:

(*a*) Normal saline/50% dextrose solution in water — any one of these could be used for diltiazem, dobutamine, dopamine, nitroglycerine, heparin, epinephrine, esmolol, theophylline, famotidine, isoprenaline, lignocaine, labetalol, magnesium sulphate, milrinone.

(*b*) 5% dextrose only should be used for nitroprusside, morphine and norepinephrine.

(*c*) Normal saline only should be used for regular insulin and amrinone.

Drugs administered only IV: adrenaline, aminophylline, protamine sulphate (all three very slowly IV), adenosine (rapid IV), alfentanil, granisetron, anistreplase, urokinase, alteplase, noradrenaline, plasma expanders, d-tubocurarine, dopamine, dobutamine, dopexamine, blood.

2. **Intramuscular (IM):** The drug is injected into the muscle mass. The common sites are deltoid, upper outer quadrant of gluteus maximus and rarely vastus lateralis.

Merits:

(1) The onset of action is quicker than by subcutaneous route as muscle is more vascular (usually).

(2) In addition to soluble drugs, mild irritants, suspensions, depot preparations and colloids can be injected.

Demerits:

(1) Pain at the site of injection is common and the possibility of abscess formation is present.

(1) Self-administration is usually not possible.

(2) In case of some drugs absorption is not reliable and, therefore, not given by this route, *e.g.*, diazepam, phenytoin, chlordiazepoxide, hydrocortisone, digoxin.

(3) Proper technique is required to avoid injury to veins, arteries or nerves.

Z-track injection: This special **IM** technique is used for **IM** injections of medications that stain the upper tissue, *e.g.*, iron dextran. The skin is displaced laterally prior to injection, the needle is then inserted and the drug injected slowly and smoothly. The needle is then withdrawn and the skin released. This creates a 'Z' pattern that blocks the infiltration of the drug into the subcutaneous tissue.

3. **Subcutaneous (SC):** Injection is made into the loose connective tissue under the skin. The common sites include outer surface of upper arm, lateral lower abdomen, front of thighs, buttocks and scapular area.

Merits:

(1) Absorption is slower than by **IM** injection as the SC tissue is less vascular. This is an advantage when one needs a prolonged and sustained action.

(2) Self-administration is possible.

Demerits:

(1) Only non-irritant drugs can be injected by this route.

(2) This route cannot be used when there is peripheral circulatory failure as in shock.

(3) Volume is usually restricted to 2 ml or less.

(4) Repeat injections at the same site can cause lipoatrophy/lipohypertrophy especially in case of insulin.

Subcutaneous fluid infusion (hypodermolysis): This is especially useful in paediatric patients and in adults with difficult or thrombosed veins. The usual dose is 75–100 ml per hour.

Advantages over IV infusion:

(1) This does not cause thrombophlebitis.
(2) It can be started in any setting.
(3) Patient mobility and comfort is greater.
(4) It is easier to maintain and re-site and requires less nursing supervision.
(5) It is less likely to cause fluid overload and pulmonary oedema.
(6) The insertion of needle is less distressing to the patients.
(7) The infusion set does not block.
(8) The cost is less.

Disadvantages over IV infusion:

(1) The volume to be given is limited to 3 litres in 24 hours.
(2) Local oedema can occur.
(3) Feeling of tightness is common.

Drugs administered subcutaneously: Adrenaline, insulin, morphine, neostigmine, local anaesthetics, bethanechol.

4. **Intradermal (intracutaneous):** The drug is injected into the layers of the skin. The usual site is medial surface of forearm. This route is mainly used for BCG vaccination, for diagnostic tests (tuberculin test, Schick test), allergic tests (test dose) and local anaesthesia.
5. **Intra-arterial:** The drug is injected into arteries. This route is useful for radiographic procedures (angiography, arteriography), regional perfusion of an area or tumour (cancer chemotherapy), and injection of streptokinase in coronary artery in acute myocardial infarction.
6. **Intrathecal (intraspinal):** The drug is injected into the subarachnoid space by lumbar puncture. The route is used for spinal anaesthesia, for radiographic procedures to visualize the spinal cord (myelography), to treat reversible spasticity associated with multiple sclerosis or spinal cord lesions with baclofen, to treat leukaemias that tend to spread to central nervous system with methotrexate, etc.
7. **Intra-articular:** The drug is injected into the joint space. The joints suitable for injection include knee, ankle, wrist, elbow, shoulder, hip and phalangeal joints. Spinal and sacroiliac joints are not suitable for this route. Repeat dose can cause painless joint destruction. Drugs usually given are corticosteroids (hydrocortisone acetate, triamcinolone acetonide) in rheumatoid arthritis.
8. **Intraperitoneal:** The drug is injected into the peritoneal cavity. The route is useful for peritoneal dialysis in acute poisoning or renal failure.
9. **Intramedullary (intraosseous):** The drug is injected into the bone marrow of sternum and tibia. The onset of action is rapid and comparable with **IV** injection. Drugs administered by this route include whole blood, normal saline and glucose especially when veins are not accessible in children.
10. **Epidural (peridural, extradural):** The drug is deposited between dura of spinal cord and periosteal lining of spinal canal. Drugs administered by this route include local anaesthetics for epidural nerve block.
11. **Intracardiac:** The injection is given directly into the heart by a long needle in 4th left intercostal space close to sternum. Adrenaline is administered by this route in case of cardiac arrest following drowning, electrocution or during anaesthesia.
12. **Intracavernous (intrapenile, intracavernosal):** The drug is injected into the corpus carvernosum, usually along the dorsolateral aspect of the proximal third of the penis using a half-inch 27-30 G needle, avoiding visible veins. The side and site has to be changed with each injection. Repeated injections may cause fibrotic reactions. Pain and priapism are common. Drugs administered by this route include phentolamine, papaverine and alprostadil.
13. **Intralesional:** The drug is given in the inflammatory areas including fatty areas of scalp

(in alopecia), dermatosis, psoriasis lesions, discoid lupus, inflamed cysts, etc. Usually corticostercoids like triamcinolone are administered by this route.

14. **Retrobulbar:** The drug is introduced behind the eyeball. The injection is given for the purpose of getting the drugs *(e.g.,* antibiotics, local anaesthetics, steroids, vasodilators) into the posterior segment of the globe and to affect the nerves and other structures in that space.
15. **Intracameral:** Injection is made directly into the anterior chamber (acetylcholine, α-chymotrypsin, carbachol, antibiotics, steroids) or directly into the vitreous chamber (amphotericin B, gentamicin, steroids). The local effect is immediate. Endophthalmitis, retinitis and fungal keratitis can be treated by this route.
16. **Subconjunctival:** The drug is injected underneath the anterior conjunctiva and probably passes through the sclera and into the eye by simple diffusion. The action of the drug is sustained. The route is used to introduce drugs, that if applied topically either do not penetrate into the anterior segment or penetrate too slowly to attain the desired concentration. Drugs administered by this route include antibiotics (for anterior segment infections), mydriatics, amphotericin B, clotrimazole, fluorouracil and anaesthetics.
17. **Sub-Tenon's injection:** The injection is made in the subtenon's capsule. Corticosteroids are usually given for the treatment of posterior uveitis by this route.
18. **Intravesical:** The injection is given directly into the bladder. BCG vaccine is administered by this route for immunotherapy in patients with cancer of bladder.

DF: Ampoules, vials, bottles/pouches (glass or plastic).

(*a*) ***Ampoules:*** These are sealed glass containers usually containing one dose. The remaining medication of once broken ampoules must be discarded and cannot be reused as it no longer remains sterile, *e.g.,* atropine, metoclopramide, ranitidine, promethazine.

(*b*) ***Vials:*** These are glass containers with hermetically (airtight) sealed rubber stoppers usually containing multiple doses of drug either in powder (to be reconstituted) or in liquid form, *e.g.,* insulin, local anaesthetics, benzathine penicillin, diclofenac. Sterile hypodermic needle is inserted through rubber stopper to withdraw a measured dose from vials.

(*c*) ***Bottles/pouches:*** These contain large volumes of drugs or IV fluids, *e.g.,* 5% dextrose, normal saline, ciprofloxacin.

B. Inhalation (Pulmonary or Intrarespiratory Route)

By this route, the drug particles are deposited directly into the lungs. Drugs may be administered in three ways:

(*i*) **Gases:** Volatile substances like gaseous general anaesthetics, vapours of liquid anaesthetics and gases like oxygen are administered with the help of face mask and endotracheal intubation tube.

(*ii*) **Aerosols:** These consist of very finely divided liquid or solid particles of drugs dispersed in gas, *e.g.,* salbutamol, beclo-methasone dipropionate, ipratropium bromide.

(*iii*) **Powders:** In this case, lactose or glucose powders are used to carry the drug, *e.g.,* disodium cromoglycate.

Absorption and disposition of inhaled drugs: Absorption is facilitated by large surface area of pulmonary alveolar membranes (50–100 square meters), limited thickness of these membranes (approx. 0.2 μ) and high blood flow to alveolar region. Nose efficiently traps particles before their deposition in the lung. Hence, mouth breathing of aerosolized particles is preferred. Particles greater than 20 μm in size are likely to be deposited in the bronchiolar epithelium and the respiratory cilia will sweep the particles back to larynx where they will be swallowed. Particles with diameter 1–5 μm are likely to

reach the smallest bronchioles and are the most effective. Only 2–10% of aerosolized drug is deposited in the lungs. Remainder is swallowed, absorbed and metabolized in the same way as oral formulation.

Merits:

(1) Onset of action is rapid.
(2) Dose required is significantly less compared to the systemic dose and hence the adverse effects are minimal.
(3) First pass effect is circumvented.
(4) Gastrointestinal degradation is avoided.

Demerits:

(1) Methods of administration are cumbersome.
(2) Ability to regulate the dose is poor. Even with best efforts, only 2–10% of the drug reaches the lungs.
(3) Drugs can cause inflammation of the respiratory tract.
(4) Overdoses are likely at times due to excessive self-medication.
(5) Obstruction of bronchi due to mucus plugs may cause failure of therapy.

DF/drug delivery systems:

(*a*) Aerosol-producing devices like metered-dose inhalers (MDI) and nebulisers.
(*b*) Dry powder inhalers (DPI) like spinhalers, rotahalers, diskhalers, aerohalers, turbohalers, acuhalers.

MDI have the advantage of being cheaper, portable and ideal for 'prn' medication. Nebulisers have the advantage of not requiring hand-breathing coordination and can be delivered by face masks to young children and older patients who are confused. Disadvantage of the MDI is that they contain chlorofluorocarbons (CFCs) as propellants which are added to improve the stability of the drug suspension and to prevent aggregation of particles. More recently, CFCs have been replaced by other innocuous propellants like hydrofluoroalkanes.

(*i*) **MDI:** These are the most widely used therapeutic aerosols due to convenience (Fig. 2.4). An MDI has two major components:

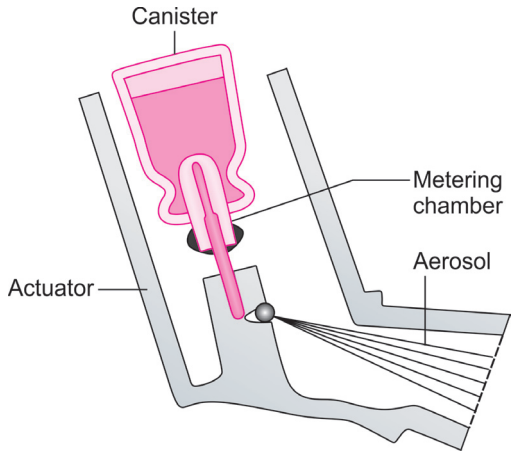

Fig. 2.4 Metered dose inhaler

(*a*) ***Canister:*** A closed plastic or metal cylinder containing propellant, active drug and metering chamber.
(*b*) ***Actuator:*** A moulded plastic container that holds the canister and directs the released aerosol towards the patient's airway.

The device is placed in front of the open mouth of the user and the canister is pushed into the actuator as a result of which a single dose of the drug is released. The puff is synchronized with the inspiration and thereafter the breath is held for 10 seconds. Thus MDI requires skillful hand-lung coordination and hence not suitable for children less than 5 years. To circumvent this difficulty, a spacer may be used.

A spacer (spacing-device) is an inflattable bag attached to the mouthpiece into which the aerosol is discharged (Fig. 2.5).

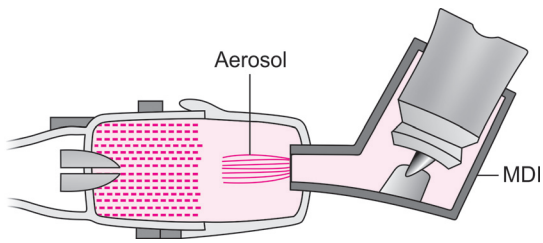

Fig. 2.5 Spacer device

Perfect synchronization with inspiration is not necessary for effective inhalation of the drug. The dose required is lesser than that with MDI alone.

(*ii*) **Nebulisers:** These are useful for those who are unable to perform proper inhalational technique. Two types are in common use: Jet and ultrasonic. In the former, the aerosol is produced by atomization of liquids by a jet of air from either a compressor or a compressed gas cylinder passing through the device (Fig. 2.6). In the latter, the aerosol is produced by the high-frequency vibrations of a piezoelectric crystal kept beneath the fluid reservoir (Fig. 2.7).

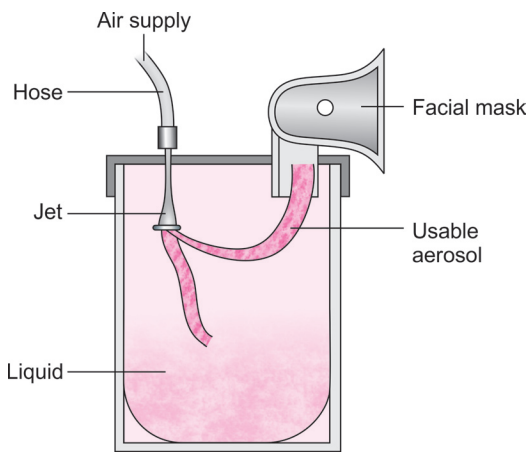

Fig. 2.6 Jet nebuliser

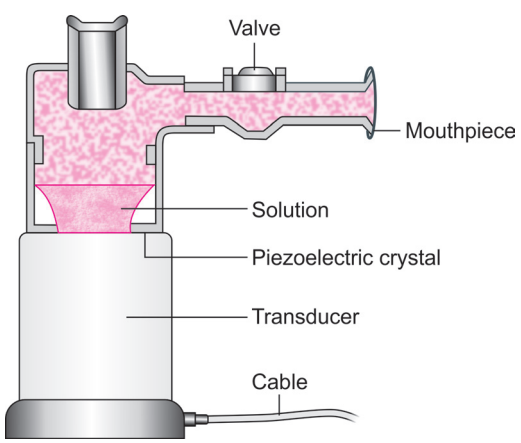

Fig. 2.7 Ultrasonic nebuliser

These are particularly useful for children under 5 years of age and in the treatment of severe asthma where respiratory insufficiency may impair inhalation from an MDI or DPI.

(*iii*) **DPI:** In these delivery systems, the drug is placed in a capsule as a fine powder in large aggregates either alone or with carrier particles usually lactose. In the device, the capsule is initially either pierced by needle (spinhaler) or sheared in half (rotahaler). During inhalation, the capsule rotates causing the powder to enter the inspired air and be broken into small particles suitable for delivery to the airways. The energy derived to disperse the powder is derived from the patient's inspiratory effort. More recently, multi-dose DPIs are available for use (diskhalers, turbohalers, etc.).

Demerits of DPI:

(1) Oesophageal irritation is common.
(2) Direct effect of powder in airways causes cough.
(3) Walls of capsule may be coated with drug as a result of failure of the aggregated powder to break up. This may cause virtually all of the drug to be deposited in the mouth.

Caution: Patients should be advised to rinse their mouths after inhaled therapy to decrease systemic absorption of drug deposited in the mouth.

C. Nasal Route

Drugs are administered via nose for systemic effect. Less than 1% dose may be absorbed. Sprays are more effective than the drops. Many drugs are better absorbed if 'promoters' are included in the formulation. These agents may alter the mucous covering of the nasal mucosa or open up the tight junctions of the epithelial cells. However, there are some concerns over local toxic effect to the mucosa with long-term use.

Drugs administered intranasally for systemic effect: Nafarelin, buserelin, budesonide, desmopressin, sumatriptan, azelastine, nicotine, oxytocin.

DF: Sprays, drops, inhalant crushable glass perles.

D. Endotracheal (Intratracheal)

Drugs are administered by means of an endotracheal tube in case of an acute emergency. Absorption is rapid and there is fast access of drug to the heart via pulmonary veins.

Drugs administered intratracheally: Adrenaline, atropine, beractant (for respiratory distress syndrome in infants).

E. Transdermal (Percutaneous)

By this route, the drug is applied to the skin in various forms for systemic effect. Absorption is generally better across thin skin *(e.g.,* behind the ear) or across the skin not regularly exposed to the environment.

Merits:

(1) Rate of delivery is steady, without any peaks or troughs.
(2) Bypasses hepatic first pass metabolism.
(3) Duration of action is prolonged.
(4) The patients can rapidly terminate the drug effect by removal of the application from the surface of the skin.
(5) The route allows convenient administration of drugs with short half-life.
(6) Patient compliance is improved.
(7) Systems are non-invasive, avoiding the inconvenience of injections.

Demerits:

(1) Passive diffusion through the skin is not practical with drugs of large molecular weight (>1000).
(2) High blood concentrations are not easily achieved.
(3) Chances of contact dermatitis or sensitization are high.
(4) Adhesiveness may vary with different skin types.
(5) The systems are relatively expensive.

DF: Transdermal delivery systems (TDS), ointments, patches.

TDS: TDS employ different designs, but in all, the delivery system contains a large drug concentration which must be maintained essentially unchanged in order to produce zero-order drug delivery. The approaches currently in use are:

(a) ***Gel matrix system:*** The drug is dispersed in the polymer gel and diffuses from the gelatinous matrix into the stratum corneum (Fig. 2.8), *e.g.,* nitroglycerine disc, nicotine patch, testosterone patch.

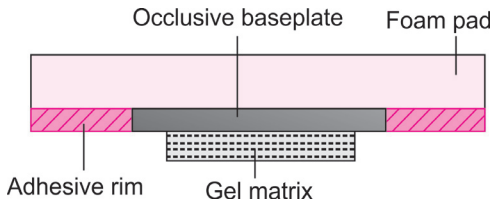

Fig. 2.8 Gel matrix system

(b) ***Fluid-filled reservoir system:*** This system contains the drug in a cream or lotion-like vehicle and, therefore, must be contained by a heat-sealed plastic envelope (Fig. 2.9), *e.g.,* estradiol, nitroglycerine, scopolamine, clonidine.

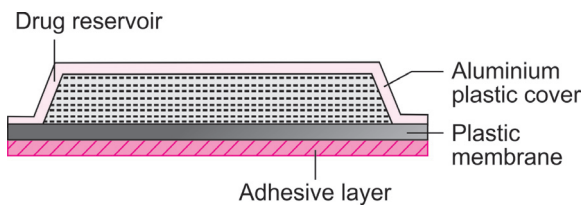

Fig. 2.9 Fluid-filled reservoir system

(*c*) ***Adhesive matrix system:*** This recent modification is composed of an impermeable backing that is coated with a drug-loaded adhesive. The backing serves as an occlusive barrier and also prevents evaporation of the drug from the system (Fig. 2.10), *e.g.,* nitroglycerine.

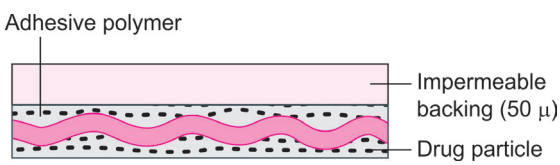

Fig. 2.10 Adhesive matrix system

Percutaneous preparations are also available in form of ointments (*e.g.,* nitroglycerine ointment 2%) for systemic use.

Factors affecting absorption of TDS:

(1) Concentration of drug in delivery system.
(2) Nature of vehicle containing the drug—vehicle having more affinity towards drugs retards the release of the drugs.
(3) Surface area of the film of drug applied to the skin—larger the area, greater is the drug release.
(4) Thickness of the film of drug applied to the skin—thicker film prolongs the release of the drug.
(5) Presence or absence of occlusion over the drug reservoir.
(6) Presence or absence of permeation enhancers (substances that increase the permeability of drug through the skin): Enhancers like acetone, dimethylsulfoxide, oleic acid, ethanol, propylene glycol increase the absorption of the drug.
(7) Nature of skin to which DF is applied:
   (*a*) Anatomical region: Different regions facilitate absorption of different drugs differently, *e.g.*, nitroglycerine, scopolamine and nicotine patches are better absorbed when applied to the chest, ear lobe and upper arm, respectively.
   (*b*) Thickness of skin: Greater the thickness, slower is the permeability.
   (*c*) Multiple applications at the same site: Permeability increases, if applied repeatedly at the same site.
   (*d*) Other factors: Presence of skin pigmentation, psoriasis, dermatitis, hydration can all affect the absorption.
(8) Metabolism of the drug in the skin.
(9) Binding of drug to epidermis.
(10) Blood supply at the site of application.

F. Topical

Drugs are applied either on the skin (dermal) or mucous membrane (mucosal) for local effect. Few drugs penetrate the intact skin but drugs may be absorbed through abraded, burnt or denuded skin and cause systemic adverse effects. Hydrated skin is more permeable than dry skin and an occlusive dressing facilitates absorption. Absorption of drug through the skin is proportional to the surface area over which they are applied and to their lipid solubility. Absorption through mucous membranes occurs readily compared to intact skin and can produce systemic toxicity.

(*i*) Dermal/cutaneous: Drugs are applied to skin for a local effect. Drugs administered topically include topical antibiotics, steroids, antifungals, scabicidals, pediculocidals, sunscreens (PABA), melanizing drugs for promoting repigmentation (methoxsalen, psoralen), emollients (to soothe, hydrate the skin), keratolytics (to soften the epidermal cells), antiacne drugs (tretinoin, benzoyl peroxide), antiseborrheics, minoxidil, heparin, allantoin, calcipotriol, etc.

DF: Lotions, liniments, ointments, pastes, creams, powders, sprays (aerosols), jellies, tinctures, gels, shampoos.

(*a*) ***Lotions:*** These are liquid preparations meant for external application without friction and containing usually protective, astringent and soothing agents, *e.g.*, calamine lotion.
(*b*) ***Liniments:*** These are liquid preparations meant for external application which are applied with friction and containing counterirritants and rubefacients to relieve pain, *e.g.*. turpentine liniment. These should not be applied to bruised or broken skin.
(*c*) ***Ointments:*** These are semi-solid preparations for external application containing a greasy base, *e.g.*, ointments containing antibiotics.
(*d*) ***Pastes:*** These are ointment-like preparations which are non-greasy due to presence of starch, *e.g.*, zinc oxide paste.
(*e*) ***Jellies:*** These are translucent, non-greasy, semisolid preparations used externally. They contain considerable amount of water and are particularly suitable as vehicles for water-soluble

medicaments such as local anaesthetics, spermicides and antiseptics. They are used for medication, lubrication and some miscellaneous uses like electrocardiography and ultrasonography.

(*f*) ***Sprays:*** These are drugs in metallic or plastic containers released on the skin with force for topical effect. Drugs administered by sprays include ibuprofen, povidone-iodine, tolnaftate, dexamethasone, dibucaine, triamcinolone, betamethasone valerate, etc.

(*ii*) Mucosal: Drugs are applied to the mucous membranes for their local effect.

(*a*) **Conjunctival:** Drugs are applied in the conjunctival sac.

DF: Ointments, drops, gels, applicaps.

Drugs: Physostigmine, atropine, pilocarpine, timolol, gentamicin, steroids, etc.

(*b*) **Intra-aural (otic):** Drugs are introduced in the ear canal.

DF: Ear drops, ear ointments, otic irrigation solutions.

Drugs: Antibiotics, antifungals, earwax softeners (paradichlorobenzene), sodium fluoride (for otosclerosis), benzocaine, cerumenolytics.

(*c*) **Nasal:** Drugs are put in the nose for local action.

DF: Drops, sprays, inhalant capsules (contents poured into hot water or handkerchief and inhaled).

Drugs: Nasal decongestants (xylo-metazoline, oxymetazoline, normal saline, naphazoline), antiallergics (azelastine, beclomethasone, etc.), anti-infectives.

(*d*) **Anorectal:** Drugs are applied externally to the perianal area or inserted in the anal canal for treating local conditions.

DF: Ointments, creams, aerosols (foams), suspensions.

Drugs: Lignocaine, framycetin, zinc oxide, hydrocortisone, mesalamine, bisacodyl, pramoxine, barium sulphate.

(*e*) **Vaginal:** Drugs are introduced into the vagina for the treatment of moniliasis, for hormone replacement therapy (in case of atrophic vaginitis) or for contraception.

DF: Pessaries, vaginal tablets, inserts, aerosols (foams), gels, jellies, creams, douches, powders, capsules.

Drugs: Povidone-iodine, clotrimazole, estradiol, conjugated oestrogens, acetic acid, terconazole, sulfathiazole, miconazole, sulfanilamide.

(*f*) **Urethral (intraurethral, transurethral):** Drugs are introduced in the urethra.

DF: Jellies, suppositories (pencil-shaped), bougies, pellets, solution.

Drugs: Lignocaine, alprostadil, sorbitol.

(*g*) **Oropharyngeal:** Drugs are applied to the oropharynx.

DF: Paints, gargles, troches (lozenges), mouth washes, pellets, gels, pastes.

Drugs: Mandl's paint, povidone-iodine gargles, dequalinium lozenges, choline salicylate, hydrocortisone succinate, amlexanox (for aphthous ulcers).

G. Newer Drug Delivery Systems

In addition to the transdermal DDS and buccal tablets, there are many new DDS. The common ones are:

(1) Intraocular: DDS is used in the eye.

(*a*) Ocusert: This device is placed directly under the eyelid to deliver pilocarpine over a period of one week.

(*b*) Hydrophilic contact lenses for pilocarpine.

(*c*) Intravitreal device for sustained ganciclovir delivery in cytomegalovirus retinitis.

(*d*) Liposome-encapsulated medication.

(*e*) Biodegradable microspheres.

(*f*) Codrugs whose chemical bonds hydrolyse slowly for controlled release of drug in the eye.

(2) Intravaginal: DDS is introduced in the vagina.

(*a*) Contraceptive ring for oestrogen/ progestins.

(*b*) Sandwich 3-layered device for oestrogen/ progestins.

(*c*) Dinoprostone vaginal insert.

(*d*) Prostaglandin release device.

(3) Intrauterine: DDS is placed in the uterus.

(*a*) **Progestasert:** This is a T-shaped progesterone containing unit which contains 38 mg of progesterone and delivers 65 µg of the drug daily for one year (Fig. 2.11).

(*b*) Encapsulated oestrogen/progestin containing device.

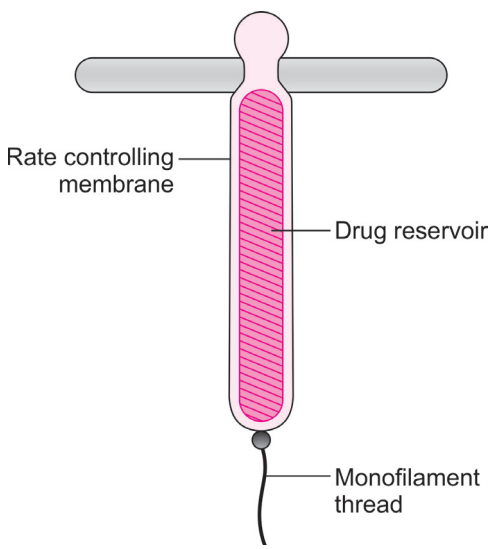

Fig. 2.11 Progestasert

(4) Subcutaneous delivery systems:

(a) Subcutaneous pumps for delivery of insulin.

(b) Jet injector system (dermojet): The drug is released from a gun and deposited SC in form of a jet.

(c) SC pen devices for insulin.

(5) Implants: These are sterile, solid drug products made by compression, melting or sintering processes. They generally consist of the drug and rate-controlling excipients.

(*a*) **Implant:** This device consists of the drug incorporated into a medical grade silastic material measuring about 34 mm long. Six capsules are placed subdermally within one week of menses, into the inner portion of upper arm. The drug is released slowly over 5 years. This is mainly used as a contraceptive.

(*b*) **Gliadel wafer implant:** This is a sterile wafer 1.45 cm in diameter and contains 192.3 mg of a biodegradable copolymer with 7.7 mg of carmustine. This is used to control local delivery of carmustine which is distributed uniformly throughout the copolymer matrix.

(*c*) **Goserelin acetate implant:** This device contains 3.6 mg of goserelin which is released slowly over a 28-day period.

(6) Targeted delivery systems:

(*a*) **Liposomal DDS:** Liposomes are composed of small vesicles of a bilayer of phospholipid encapsulating an aqueous space ranging from about 0.03 to 10 µ in diameter. They are composed of one or many lipid membranes enclosing discrete aqueous compartments. The enclosed vesicles can encapsulate water-soluble drugs in the aqueous spaces and lipid-soluble drugs can be incorporated into the membranes. Liposomes can be administered parenterally (usually IV), topically, by inhalation or possibly by other routes. Drugs administered by liposomal DDS include amphotericin B and anticancer agents.

Merits:

(1) Drugs in liposomes are delivered intact to various tissues and cells, thus enabling site-specific drug delivery.

(2) Both hydrophilic and lipophilic drugs can be carried.

(3) Other tissues and cells of the body are protected from the drug until it

is released by the liposomes, thus decreasing the drug's toxicity.

Demerits:

(1) Liposomes may be rapidly removed from circulation by the cells of the reticuloendothelial system.

(2) Liposomes may be taken up by phagocytes thus delaying the release of the drug.

(*b*) **Nanoparticles:** These are microcapsules containing the dispersed drug with diameter of 200–300 nm and administered IV.

(*c*) **Monoclonal antibodies:** These invade cancer cells and deliver lethal concentrations of drug to the cancer tissue.

(*d*) **Reseated erythrocytes:** Drugs are entrapped in erythrocytes and suspended in hypotonic medium and administered I.V.

(7) Transurethral system (MUSE microsuppository): This urethral microsuppository is a single use medicated system for the delivery of alprostadil to the male urethra. The microsuppository measuring 1.4 mm in diameter and 3–6 mm in length resides in the tip of a translucent hollow applicator. It is administered by inserting the applicator tip into the urethra after urination. It is indicated for erectile dysfunction.

(8) Self-regulatory delivery systems: These can deliver the drug at a rate according to the needs of the body. These are of two types: modulated and triggered. Modulated devices release the drug continuously at a rate controlled by the concentration of an external stimulus. Triggered devices do not have a basal drug release. The drug is only released when the system is activated by a stimulus.

DOSAGE FORMS: INSTRUCTIONS TO PATIENTS

I. Eye Drops

(1) Wash your hands.
(2) Do not touch the dropper opening.
(3) Look upward.
(4) Pull the lower eyelid down to make a 'gutter'.
(5) Bring the dropper as close to the 'gutter' as possible without touching it or the eye.
(6) Apply the prescribed amount of drops in the 'gutter'.
(7) Close the eye for about 2 minutes.
(8) Do not shut the eye too tight.
(9) If more than one kind of eye drops are used, wait at least 5 minutes before applying the eye drops of the other drug.

II. Nasal Drops

(1) Blow the nose.
(2) Sit down and tilt head slightly or lie down with a pillow under the shoulders.
(3) Keep head straight.
(4) Insert the dropper one cm into the nostril.
(5) Apply the amount of drops prescribed.
(6) Immediately afterward tilt head forward slightly.
(7) Sit up for a few seconds, the drops will then drip into the pharynx.
(8) Repeat for the other nostril, if necessary.

III. MDI/DPI

(1) Cough up as much sputum as possible.
(2) Shake the MDI before use or place the capsule in the DPI.
(3) Place the lips tightly around the mouthpiece.
(4) Tilt the head backward slightly.
(5) Breathe out slowly, emptying the lungs of as much air as possible.
(6) Breath in deeply and activate the MDI/DPI, keeping the tongue down.
(7) Hold the breath for 10–15 seconds.
(8) Breath out through the nose.
(9) Rinse the mouth with warm water.

IV. Suppository

(1) Wash your hand.
(2) Remove the wrapper.
(3) Moisten the suppository with cold water.
(4) Lie on your side and pull up your knees.

(5) Gently insert the suppository into the anal canal rounded end first.
(6) Remain lying down for a few minutes.
(7) Try not to have bowel movement during first hour.

V. Vaginal Tablets

(1) Wash your hands.
(2) Remove the wrapper.
(3) Place the tablet into the open end of the applicator. If no applicator is provided, dip the tablet in lukewarm water just to moisten it.
(4) Lie on your back, draw your knees up a little and spread them apart.
(5) Gently insert the applicator with the tablet in front (or the tablet itself) into the vagina as far as possible.
(6) Depress the plunger so that the tablet is released.
(7) Withdraw the applicator.
(8) Clean both parts of the applicator thoroughly with soap and boiled lukewarm water.

VI. Subcutaneous Injection

(1) Wash your hands.
(2) Disinfect the skin with spirit.
(3) 'Pinch' fold of the skin.
(4) Insert the needle in the base of the skin fold at an angle of 20–30°.
(5) Release the skin.
(6) Aspirate briefly and inject slowly over 0.5 to 2 minutes.
(7) Withdraw needle quickly.
(8) Press sterile cotton wool onto the opening.

VII. Transdermal Drug Delivery System

(1) Preferred general application site is usually stated in the package insert for each product. Rotate the locations within that site. Skin site may be reused within a week.
(2) See that the skin is dry and clean, free of hair, not oily, inflamed, broken or calloused — wet skin may increase permeability causing toxicity.
(3) Do not physically alter the TDDS by cutting.
(4) Wash your hands.
(5) Remove the protective backing of the system.
(6) Press firmly against the skin site with the heel of the hand for about 10 seconds to assure uniform contact and adhesion.
(7) Do not place at a site that is subject to being rubbed off by clothing.
(8) The system can be left on during bath or swim.
(9) Wear for full period of time and then remove and replace.
(10) Used system containing residual drug should be discarded in a manner safe to pets and children.

❍❍❍

FIND OUT

1. How do you use a nasal spray?
2. What is dose-dumping?
3. What are pulvules?
4. How can you minimise the local adverse effects of transdermal patches?
5. What is the risk of using IM route of injection in patients put on anticoagulants?

3

Clinical Pharmacokinetics

LEARNING OBJECTIVES

- Processes involved in pharmacokinetics of drugs
- Mechanisms of drug passage across cell membranes
- Bioavailability and factors affecting it
- Implications of protein binding of drugs
- Process of biotransformation and factors affecting it
- Routes of drug excretion and half-life

Pharmacokinetics is 'what the body does to the drug'.

A. ABSORPTION OF DRUGS

Mechanisms of Drug Passage Across Cell Membranes

(1) **Convective flow (solvent drag):** In this mechanism the dissolved solutes are 'dragged' by the bulk water flow (as seen in the renal epithelium) and the blood flow (as seen in blood vessels).

(2) **Simple (passive) diffusion:** This is the most important method of drug transfer. No energy is required. The net transfer is directly proportional to the concentration gradient. The transport occurs through the semipermeable membrane. Aqueous solution of drug molecules diffuses through the membrane by first dissolving in the aqueous portion of the membrane and then by dissolution in the lipid portion of the membrane. Lipid-soluble drugs are absorbed more rapidly by this method.

(3) **Channel-mediated diffusion (diffusion through aqueous pores or pore transport):** The transport of drugs takes place through pores of biological membranes. Only compounds with molecular weight <100 D can be absorbed. This mechanism is mainly important in kidney and partially in jejunal epithelium.

(4) **Carrier-mediated (facilitated) diffusion (uniport):** Energy is not required for this transport. Presence of carrier is mandatory. The solute binds to the carrier protein and is transferred across the cell membrane down the electrochemical gradient. This mechanism is seen in renal tubules, biliary tract, blood–brain barrier and gastrointestinal tract. Drugs

transported by this method include vitamin B_{12},l-dopa, iron, calcium, etc.

(5) **ATP-mediated transport (primary active transport):** This is an active transport mechanism where drugs are transported against the concentration gradient (uphill). ATP is hydrolysed to ADP causing conformational change in the solute thus providing necessary energy for transfer. Drugs resembling natural substrates are transported this way. Renal tubular secretion of weak acids and bases also involves active transport. Drugs transported by this method include methyl-dopa, l-dopa, 5-fluorouracil, methotrexate, etc.

(6) **Ion-pair transport:** This involves transport of charged molecules due to the formation of a neutral complex with another charged molecule carrying an opposite charge. The neutral ion-pair is transported across the membrane by passive diffusion. Highly ionized organic compounds (ions) appear to combine with endogenous substances of gastrointestinal tract which carry an opposite charge to form an ion-pair. Drugs forming ion-pairs include quinine (with hexylsalicylate) and propranolol (with oleic acid).

(7) **Symport (co-transport):** This involves simultaneous transport of solute species with a second solute travelling uphill against concentration gradient along with first solute. This is primarily seen in kidneys.

(8) **Antiport (countertransport):** This involves transportation of two solutes simultaneously, one against concentration gradient and the second along the concentration gradient. This mechanism is significant in the kidneys.

(9) **Pinocytosis (corpuscular, vesicular or particulate absorption):** In this mechanism, drugs or compounds do not have to be in aqueous solution in order to be absorbed. Non-aqueous liquid droplets or solid particles are engulfed by processes formed by the epithelial cells thereby forming a vacuole or vesicle. This transport is important for the absorption of vitamins A, D, E, K, uptake of fatty acids, fats and amino acids. This is not very significant for drugs.

Bioavailability

Definition: It is the rate and extent of absorption of drugs from a given dosage form into the systemic circulation.

Factors Affecting Bioavailability

I. Physical properties of the drug:

(*a*) ***Physical state of the drug:*** Gases are absorbed faster than liquids.

(*b*) ***Lipid solubility:*** As cell membranes are lipid in nature, lipid solubility favours absorption. Lipophilic drugs like benzodiazepines, doxycycline, propranolol are better absorbed.

(*c*) ***Ionisation:*** In general, unionized drugs being more lipid soluble are better absorbed. Ionised drugs like aminoglycosides are not absorbed.

(*d*) ***pH:*** Acidic drugs like salicylates and barbiturates are better absorbed in acidic medium. Basic drugs like pethidine, ephedrine are better absorbed in the alkaline medium of the ileum.

(*e*) ***Vehicle in the DF:*** Drugs in aqueous solution are more rapidly absorbed than those given in oily solution.

II. Formulation and characteristics of the drug product (pharmaceutical factors):

(*a*) ***Particle size of the drug:*** In order for a drug to be absorbed, it must first be dissolved in the fluid at the absorption site. Therefore, the particle size of the drug powder used in the formulation of a solid or semi-solid DF can have a significant effect on the availability of the drug from the DF, especially in those cases where the drug is poorly water soluble, *e.g.*, griseofulvin.

(*b*) ***Crystalline properties of the drug:*** In general, amorphous forms possess greater solubility and faster dissolution than the crystalline forms.

(*c*) ***Salt form of the drug:*** Most drugs are either weak organic acids or weak organic bases and are poorly water-soluble. The salt forms

of these drugs possess much greater rate and extent of solubility than their respective free acids or bases. Sodium and potassium salts are generally used in the preparation of DF of weak organic acids, *e.g.*, phenytoin sodium. Hydrochloride, sulphate and phosphate salts are used for weak organic bases, *e.g.*, tetracycline hydrochloride.

(*d*) ***Adjuncts in tablets/capsules (formulation factors):*** Inactive and inert ingredients (excipients, adjuncts, others) present in the DF can affect bioavailability. Most common adjunct shown to influence availability is magnesium stearate. It can coat drug particles, if used in larger quantity than recommended. This coating is water repellant and renders the drug particles impermeable to the dissolution medium. Some excipients form a complex with drugs rendering it unavailable for absorption, *e.g.*, dicalcium phosphate interferes with tetracycline.

(*e*) ***Tablet hardness and tablet disintegration time:*** Disintegration time of tablet depends on tablet hardness (pressure used during compression). Higher the force of compression, difficult is the disintegration. Faster disintegration leads to faster dissolution. Disintegrating agents when used cause the tablet to disintegrate completely regardless of hardness.

(*f*) ***Tablet coatings:*** Coating may release the drug unevenly or not at all. The coating may not dissolve and the DF may be excreted without any therapeutic benefit.

III. Patient characteristics:

(*a*) ***pH of lumen:*** Acidic pH of stomach favours absorption of acidic drugs like penicillins, indomethacin, thiazides, furosemide, aspirin, phenylbutazone, acetazolamide and barbiturates. Alkaline pH of small intestine favours absorption of basic drugs like dopamine, pethidine, morphine, quinine, amiloride, triamterene, reserpine, atropine, quinidine and ephedrine.

(*b*) ***Gastric emptying time:*** Trauma, pain, labour can decrease GET thereby increasing absorption of drugs from ileum. Similarly duodenal ulcer and coeliac disease can delay absorption from intestine by increasing GET.

(*c*) ***Intestinal transit time:*** Increased peristaltic activity can decrease absorption by decreasing the transit time.

(*d*) ***Area of absorptive surface:*** Absorption is more rapid from larger surface areas like pulmonary alveolar epithelium, intestinal mucosa and skin.

(*e*) ***Gastrointestinal disease:*** Coeliac disease, malabsorption syndrome, pancreatic disease, hepatic dysfunction all decrease the absorption of lipophilic drugs.

(*f*) ***Mesenteric blood flow:*** Heavy carbohydrate meals and hypovolemic states decrease the mesenteric blood flow thereby decreasing absorption.

(*g*) ***Circulation to site of absorption:*** Massage or local application of heat increases blood flow thereby increasing absorption. Use of vasoconstrictors and shock can decrease blood flow and decrease absorption.

(*h*) ***Enterohepatic circulation:*** This can delay the absorption of certain drugs like estradiol, phenolphthalein.

(*i*) ***Surgical interference with gastric function:*** Gastrectomy decreases absorption of digoxin, 1-dopa, sulfonamides, ethambutol, ethionamide, iron and folic acid.

IV. Presence of other substances in gastrointestinal tract:

(*a*) ***Interaction with other drugs/ions:***

(*i*) Drugs can affect the absorption of other drugs by increasing (*e.g.*, metoclopramide) or decreasing (*e.g.*, atropine) the gastric emptying.

(*ii*) Cholestyramine decreases absorption of digoxin, warfarin, thyroxine; para-amino salicylic acid decreases absorption of rifampicin and INH; vitamin C increases absorption of iron.

(*iii*) Alteration of bowel flora especially by antibiotics can decrease absorption.

Table 3.1 Effect of food on bioavailability of drugs

1. Increased	Doxycycline, carbamazepine, cefuroxime axetil, cefpodoxime proxetil, propranolol, griseofulvin, phenytoin, chloroquine, riboflavin, lithium, nitrofurantoin, spironolactone, hydralazine, hydrochlorothiazide, halofantrine, ticlopidine, metoprolol, labetatol,
2. Decreased	Ampicillin, aspirin, roxithromycin, INH, captopril, 1-dopa, oxytetracycline, penicillin, rifampicin, carbenicillin, cloxacillin, norfloxacin, ofloxacin, azithromycin, erythromycin (base/stearate), chloramphenicol, lincomycin, barbiturates, digoxin, sotalol.
3. Delayed	Paracetamol, cephalexin, ciprofloxacin, cefaclor, trandolapril.
4. Unaffected	Penicillin V, amoxycillin, bacampicillin, lomefloxacin, clarithromycin, metronidazole, theophylline, erythromycin estolate/ethylsuccinate, clindamycin, atenolol, acebutolol, pindolol, prednisone, enalapril, lisinopril.

(*b*) *Presence of food:*

(*i*) Food may increase, decrease, delay or have no consistent effect on absorption of drugs (Table 3.1).

(*ii*) Type of food: Calcium rich food decreases absorption of tetracyclines; fatty meals increase absorption of albendazole and mebendazole.

V. Pharmacokinetic characteristics of drugs:

(*a*) Drug metabolism by gut bacteria:

(*i*) Production of penicillinase may break-down the antibiotics like benzyl penicillin.

(*ii*) Activity of sulfasalazine and olsalazine is increased by bacteria and gut flora by converting them to active sulfide moiety.

(*iii*) Digoxin, 1-dopa and morphine may be partly or wholly metabolized by gut flora.

(*b*) Drugs like isoprenaline can be metabolized in the gut wall.

Table 3.2 Drugs showing extremes of oral absorption

1.	**Oral absorption and bioavailability 90–100%**
	Isosorbide-2-mononitrate, sulfamethoxazole, valproic acid, sotalol, phenylbutazone, ofloxacin, phenobarbitone, minocycline, ketoprofen, ketorolac, lithium, chlordiazepoxide, cefadroxil, diazepam, metronidazole, naproxen, clonazepam, gemfibrozil, indomethacin, amoxycillin, paracetamol, clonidine, dapsone, ibuprofen, imipramine.
2.	**Drugs not absorbed orally**
	Adrenaline, noradrenaline, dopamine, dobutamine:, aminoglycosides, parenteral cephalosporins, imipenem, azlocillin, amphotericin B, alfentanil, alcuronium, heparin, insulin, idoxuridine.

(*c*) Drugs like nitroglycerine, isosorbide dinitrate are metabolised in the liver during their first pass thereby reducing the bioavailability.

(*d*) Some drugs like benzyl penicillin, insulin, oxytocin, vasopressin and heparin are destroyed in gastric acid and availability is low, if given orally.

B. DISTRIBUTION OF DRUGS

Regardless of route of administration, after its appearance in bloodstream, part of the drug starts undergoing elimination via an excretory mechanism and part of the drug begins distributing into the various body fluids and tissues. In addition to distribution primarily in plasma fluid, a lot of drugs are also distributed in extracellular body water and tissues like adipose tissue, muscles, bones, hair, etc. The extent of distribution is dependent on the relative affinity of the drug towards a particular tissue. For drugs which exhibit extensive tissue distribution, a higher dose may be needed to achieve the desired therapeutic concentration of the drug in the plasma.

Plasma Protein Binding

Drugs are transported from site of administration to the receptor sites by plasma proteins. Most of the drugs bind reversibly to serum albumin. Basic drugs like quinidine, chlorpromazine and imipramine bind to α1-acid glycoprotein. Globulin binds the sex hormones and thyroxine. Drugs also bind to α and β lipoproteins, transferrin and haemoglobin. Plasma proteins are structures with clefts and holes that can allow entry of small molecules into their

Table 3.3 Drugs and their plasma protein binding

A.	**Highly protein bound (>90%)**
	Diazepam, digitoxin, warfarin, chlorambucil, amiodarone, diclofenac, fluoxetine, furosemide, ceftriaxone, indomethacin, spironolactone, nifedipine, naproxen, ketoconazole, ibuprofen, amitriptyline, glyburide, isotretinoin, itraconazole, ketorolac, pimozide, buprenorphine, amlodipine, chlorpromazine, felodipine, flurbiprofen.
B.	**Low protein bound (<10%)**
	Atenolol, amikacin, ganciclovir, gentamicin, lomefloxacin, netilmicin, pancuronium, pyrazinamide, tobramycin, zalcitabine, insulin, l-dopa, vancomycin, cefadroxil, ampicillin, amoxycillin, metronidazole, ranitidine, ceftazidime.
C.	**Not protein bound**
	Paracetamol, isosorbide-5-mononitrate, lisinopril, sotalol, ethosuximide, kanamycin, lithium, carboplatin, gabapentin, pentoxiphylline, minoxidil, allopurinol.
D.	**Dose-dependent binding**
	Azithromycin (7–50%), tacrolimus (75–99%), disopyramide (55–80%), salicylic acid (decreases at higher doses).

interior areas. Serum albumin, the most important protein has affinity for acidic drugs like warfarin, non-steroidal anti-inflammatory drugs, penicillins and sulfonamides. Two binding sites are seen for acidic drugs on the surface of serum albumin.

Site I is less specific (warfarin site) which binds warfarin, phenylbutazone, phenytoin, valproic acid, sulfonamides, furosemide, nalidixic acid, oxyphenbutazone, tolbutamide, glibenclamide and bilirubin.

Site II is more specific (diazepam site) which binds benzodiazepines, ibuprofen, ketoprofen, ethacrynic acid, probenecid, cloxacillin, naproxen and tryptophan. Salicylic acid binds to both sites with equal affinity.

Pharmacological Implications of Protein Binding

(1) Drug particles form a drug-protein complex which is reversible, by interacting with the plasma proteins. This complex is unable to cross the cell-membranes and acts as a store of the drug. Only unbound drug can diffuse into the tissues. The bound drug can later slowly become unbound and available for action.

(2) Since drug binding is a non-selective process, many drugs can compete with each other and with endogenous substrates for the binding sites and cause displacement, *e.g.,* displacement of bilirubin by sulfonamides.

(3) Only unbound drug can be metabolised and excreted. The action of highly protein bound drugs is thus prolonged as the bound drug slowly becomes free and only then can be metabolised and excreted.

(4) In pregnancy, there is hypoproteinaemia which results in low binding. Thus normal dose of a drug will cause higher free levels and toxicity. The doses have to be, therefore, decreased in pregnancy. Similar problem can occur in chronic renal failure, chronic liver disease, nephrotic syndrome, protein malnutrition, etc., (Table 3.4).

Table 3.4 Conditions capable of altering the plasma proteins

1. Decrease in plasma proteins
(a) Albumin: Pregnancy, burns, cystic fibrosis, nephrotic syndrome, chronic liver disease, protein-losing enteropathy, chronic renal failure, trauma.
(b) α1-acid glycoprotein: Nephrotic syndrome.
2. Increase in plasma proteins
(a) Albumin: Hypothyroidism.
(b) α1- acid glycoprotein: Coeliac disease, Crohn's disease, renal failure, myocardial infarction, trauma.

(5) Displacement reactions are likely to occur in highly protein bound drugs. In drugs like warfarin (99% bound, 1% free), even 1% displacement can double the free levels of the drug causing toxicity.

(6) Penetration into the central nervous system is diminished in highly protein bound drugs.

Redistribution

Highly lipid-soluble drugs rapidly cross the blood–brain barrier and are distributed to the vascular tissues of the brain. The drug is then redistributed first to tissues with large blood flow (liver, kidneys) and more slowly to muscle. The central action is thus terminated quickly. Drugs showing this unique phenomenon include the IV anaesthetics thiopentone and methohexitone, both of which are indicated in induction of anaesthesia.

Volume of Distribution

This is a hypothetical volume of body fluid that would be required to dissolve the total amount of drug at the same concentration as that found in the blood, plasma or serum.

Steady State

This is the level of drug concentration in blood and tissue upon multiple dosing when input and output are at equilibrium, *i.e.,* the system attains a dynamic equilibrium.

Loading Dose

Most drugs for chronic conditions are prescribed in a dosage regimen which is based on the administration of a fixed constant dose of a drug administered at fixed regular dosing intervals for relatively long periods of time. If the time to reach steady state concentration of the drug in the plasma represents an unacceptable delay *(e.g.,* in the case of acute illness, serious illness and/or drugs with a long half life), then a loading dose is usually recommended. The main purpose of a loading dose is to attain a steady-state concentration of the drug as quickly as possible, usually right from the start of the dosage regimen for the treatment. Chloroquine and digoxin are given by a loading dose.

Cerebrospinal Fluid Entry of Drugs

Entry of drugs into the central nervous system is dependent on lipid solubility. Highly lipid-soluble drugs are taken up very first. The endothelial cells of the CNS are joined together by tight junctions that limit the entry of water-soluble drugs. Drugs also gain access to CNS by way of the choroid plexuses. Each choroid plexus is composed of a network of small blood vessels and capillaries projecting into a ventricular space and covered by a layer of epithelial cells specifically adapted for the secretion of CSF. Diffusion of drugs across the choroid plexus and into the CSF is largely restricted to highly lipid soluble drugs.

Therapeutic Ramifications of CNS Entry

(1) Some drugs intended for peripheral nervous system effects may cause CNS disturbances on entry into the brain. Modifications of such drugs (*e.g.,* scopolamine to methscopolamine) will prevent CNS effects while maintaining the peripheral actions.

(2) Some drugs are not allowed entry into the CSF under normal meningeal condition and can be used for systemic conditions without central interference. However, the capillary permeability in the brain increases during meningeal inflammation and the drug can be used for meningitis, *e.g.,* Penicillin G.

(3) In the treatment of parkinsonism, a disease associated with deficiency of dopamine, replacement therapy with dopamine is ineffective as it does not enter the blood–brain barrier. Instead, 1-dopa is used. L-dopa readily enters the brain and is converted to dopamine there (Table 3.5).

C. BIOTRANSFORMATION (METABOLISM)

In general, water-soluble (polar) drugs are mainly excreted unchanged by the kidneys without any biotransformation. Lipid-soluble drugs are initially filtered in glomeruli and may be fully reabsorbed. They have to be metabolised into polar compounds before excretion. The main site of metabolism is in the liver but it may also occur in the lung, kidneys, blood, brain, skin and the gut wall.

General Types of Biotransformation

(1) Active drug → Inactive metabolite
Most of the drugs follow this pattern, *e.g.*, morphine sulphate → morphine glucuronide.

Table 3.5 CSF penetration of drugs

1.	**CSF penetration high**
	Chloramphenicol, benzodiazepines, antipsychotics, propranolol, doxycycline, acyclovir, pyrimethamine, amantadine, amitriptyline, buspirone, antiepileptics, cimetidine. diphenhydramine, hydralazine, 1-dopa, lignocaine, lithium, metronidazole, alfentanil, fentanyl, indomethacin, sulfonamides, trimethoprim, fluconazole, flucytosine, pyrazinamide.
2.	**CSF penetration only if meninges are inflamed**
	Amoxycillin, ampicillin, azlocillin, benzylpenicillin , carbenicillin, cephalosporins IIIrd generation, ciprofloxacin, ofloxacin, pefloxacin, ethambutol, ketoconazole, lincomycin, imipenem, meropenem, rifampicin, aztreonam.
3.	**No CSF penetration**
	Mefloquine (although lipophilic), carbidopa, erythromycin, aminoglycosides, vancomycin, polymyxin, amphotericin B.

(2) Active drug → Active metabolite → Inactive metabolite (IaM)
e.g., amitriptyline → nortriptyline → IaM; Imipramine → desipramine → IaM; Diazepam → oxazepam → IaM; Propranolol → 4-hydroxypropranolol → IaM; Spironolactone → canrenone → IaM; Procainamide → n-acetylprocainamide → IaM; Tamoxifen → 4-hydroxy tamoxifen → IaM.

(3) Inactive prodrug → Active drug → Inactive metabolite
e.g., Prednisone → prednisolone → IaM.
Enalapril → enalaprilat → IaM.
L-dopa → dopamine → IaM.
Zidovudine → zidovudine triphosphate → IaM.
Azathioprine → mercaptopurine → IaM.
Talampicillin → ampicillin → IaM.

(4) Drug → Inactive metabolite (normal dose) → Active toxic metabolite (toxic dose)
Drugs like paracetamol when used in very high doses (for suicidal purposes or accidental ingestion by children) can be converted to toxic metabolite due to saturation of normal metabolic pathways.

(5) Inactive drug → Active drug → Toxic metabolite
Drugs like cyclophosphamide can be converted to toxic metabolite which is harmful. Cyclophosphamide → 4-hydroxycyclo-phosphamide → acrolein (toxic to bladder).

(6) Drug → Active carcinogen
These drugs are not used in therapeutics.

Specific Patterns

Biotransformation involves two types of biochemical reactions: Phase I and Phase II. These reactions often (not always) occur sequentially. In phase-I reaction, a drug undergoes either oxidation, reduction or hydrolysis to form more reactive, sometimes toxic products, which are further metabolised by phase II reactions.

Phase II reactions involve the conjugation reactions which usually convert the drug or the phase-I product into inactive, readily excretable compound. These reactions take place mainly in liver, although other tissues may be involved, *e.g.*, suxamethonium in plasma, prostanoids in lung, salbutamol in the gut wall. The reactions are brought about by microsomal enzymes attached to smooth endoplasmic reticulum.

Phase I Reactions

(1) **Oxidative reactions:** These include hydroxylation of H and C atoms, dealkylation, deamination and oxidation. The reactions are catalysed by complex enzyme system called mixed function oxygenase system. Most important enzyme superfamily involved is cytochrome P-450 (microsomal). Other enzymes that have a role to play include alcohol dehydrogenase (for alcohol), xanthine oxidase (for 6 mercaptopurine) and monoamine oxidase (for noradrenaline).

Examples:

(*i*) *N-dealkylation:* Diazepam, imipramine, theophylline, erythromycin, morphine.

(*ii*) *O-dealkylation:* Codeine, indomethacin.
(*iii*) *Aliphatic hydroxylation:* Tolbutamide, midazolam, ibuprofen, cyclosporine.
(*iv*) *Aromatic hydroxylation:* Phenytoin, propranolol, warfarin, amphetamine.
(*v*) *Deamination:* Diazepam, amphetamine.
(*vi*) *N-oxidation:* Dapsone, chlorpheniramine, thioridazine.
(*vii*) *S-oxidation:* Chlorpromazine, omeprazole.

(2) **Reduction:** These reactions are less common. Microsomal enzymes are involved here also. ***Examples:*** Warfarin, nitroglycerine, prednisone, cortisone.

(3) **Hydrolytic reactions:** These do not involve hepatic microsomal enzymes. They occur in plasma and tissues due to action of esterases and amidases.
Examples:
(*i*) *Ester hydrolysis:* Clofibrate, procaine, aspirin.
(*ii*) *Amide hydrolysis:* Lignocaine, procainamide, indomethacin.

Cytochrome P-450 Superfamily (CYP)

- CYPs involved in drug metabolism fall into families 1, 2 and 3.
- In humans, 12 CYPs are important for drug matabolism — CYP 1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C 19, 2E1, 3A4 and 3A5.
- The largest number of these enzymes are seen in the liver, thus ensuring efficient first-pass metabolism.
- CYPs are also expressed in GIT and in lesser amounts in kidney, lung and CNS.
- The most active CYPs for drug metabolism are in the subfamilies CYP2C, CYP2D and CYP3A.
- CYP3A4, the most abundantly expressed CYP in liver is involved in the metabolism of over 50% of drugs.
- CYPs have an unusual feature of extensive overlapping substrate specificities leading to drug-drug interactions. When 2 co-administered drugs are both metabolized by a single CYP, they compete for binding to the enzyme's active site. This results in inhibition of metabolism of one of the drugs leading to increased plasma levels.

Phase II Reactions

Energy is required to bring about these reactions. If a drug molecule has hydroxyl, thiol or amino group resulting from phase I reaction or which the drug possesses anyway, the product or the drug is susceptible for conjugation. The resultant product is inactive and is excreted in the urine.

In conjugation, the drug or phase I product combines with various chemical groups including glucuronyl (commonest), sulphate, methyl, acetyl, glyceryl and glutamyl. The glucuronyl conjugation (glucuronidation) is the only phase II reaction catalysed by microsomal enzymes (glucuronyl transferases). Other synthetic reactions are catalyzed by non-microsomal transferase enzymes.

Conjugation with glutathions is unusual in that it is directed against highly reactive metabolites like epoxides and quinones. Although a minor pathway, glutathione conjugation may be of major importance in preventing metabolism-induced drug-toxicity.

Examples:
(*i*) *Glucuronidation:* Acetaminophen, morphine, diazepam, salicylic acid.
(*ii*) *Sulphation:* Steroids, methyldopa.
(*iii*) *Acetylation:* Sulfonamides, dapsone, clonazepam, isonicotinic acid hydrazide.
(*iv*) *Methylation:* Norepinephrine, dopamine, thiouracil, captopril, methyldopa.
(*v*) *Glutathione conjugation:* Paracetamol, ethacrynic acid.
(*vi*) *Glycine conjugation:* Salicylic acid, benzoic acid, nicotinic acid.

Hepatic Clearance (HC)

This signifies the volume of drug containing plasma that is cleared by the liver per unit time. Blood enters the liver by the hepatic portal vein and hepatic artery, and leaves the liver by the hepatic vein. After oral drug administration, the drug is absorbed from gastrointestinal tract into the mesenteric vessels and proceeds to the hepatic

portal vein, to the liver and then to the systemic circulation.

The liver has the intrinsic ability to remove the drug independently of blood flow. This is called intrinsic clearance (IC). This is primarily due to the inherent ability of biotransformation enzymes (mixed function oxidases) to biotransform the drug as it enters the liver. IC depends also on the concurrent administration of other drugs. Some drugs increase the activity of these enzymes (enzyme induction) and some do the opposite (enzyme inhibition).

HC also includes the excretion of the drug into the bile by active transport or by enterohepatic circulation. HC may be affected by the blood flow to the liver. Increased blood flow will increase the rate of removal of the drug. Drugs like propranolol, disease states and exercise can alter the blood flow (normal blood flow is 1.5 litres per minute) and affect HC.

The fraction of drug removed from plasma by the liver is called hepatic extraction ratio (HER). This is obtained by dividing the amount of drug removed from plasma by the amount of drug contained in the plasma as it enters the liver. HER ranges from 0 (no drug removed by liver) to 1 (entire quantity removed). A value of <0.2 is considered as low (more drug available for action) whereas a value of >0.7 is considered as high (drugs are not given orally). HER of commonly used drugs is given in Table 3.6.

Table 3.6 Hepatic extraction ratio of commonly used drugs

(*a*) HER >0.5 →	Lignocaine, nitroglycerine, propranolol, pethidine, pentazocine, nortriptyline, morphine, labetalol, verapamil, metoprolol, imipramine.
(*b*) HER <0.5 →	Phenytoin, diazepam, tolbutamide, warfarin, digitoxin, theophylline, paracetamol, chlorpromazine, chloramphenicol.

First Pass Effect (Presystemic Elimination)

A portion of the orally administered drug undergoes elimination before it has a chance to be absorbed. This is called first pass effect. Drugs exhibiting high first pass effect are best administered by routes other than involving absorption through the gastrointestinal tract. A variety of factors contribute to the first pass effect like:

(*a*) Metabolism of drug by intestinal flora, *e.g.*, digoxin, L-dopa, morphine.
(*b*) Metabolism in the gut wall, *e.g.,* isoprenaline, paracetamol, ethinylestradiol, cyclosporine.
(*c*) Metabolism/destruction in the gastric acid, *e.g.,* insulin, benzylpenicillin, oxytocin, vasopressin, heparin.
(*d*) Biliary excretion of the drug.
(*e*) Rapid biotransformation of the drug by the liver enzymes (high HER).

Metabolism in Other Tissues

In addition to major site of biotransformation (liver) and the minor sites of presystemic elimination (gut wall, intestinal flora, etc.), drugs may be metabolised by other tissues as follows:

(*i*) **Metabolism in the kidneys:** Enzymes in the renal cortex and medulla are known to metabolise certain drugs, *e.g.*, desipramine, morphine, imipenem, zidovudine, meropenem.
(*ii*) **Metabolism in the skin:** Few drugs are metabolised in the layers of the skin, *e.g.*, estradiol, hydrocortisone, progesterone, testosterone, vidarabine.
(*iii*) **Metabolism in the lung:** Studies have shown that the lung is a primary site for metabolism of endogenous compounds such as bradykinin, angiotensin I, prostaglandins and biogenic amines.

Factors Affecting Biotransformation

(1) **Age:** In neonates and elderly, the rate of metabolism is decreased.
(2) **Gender:** In general, metabolism is decreased in females, but increased in pregnancy.
(3) **Liver disease:** The rate of elimination is decreased in hepatic disease. Thus there is increased bioavailability in drugs with high HER. Accumulation of drugs can cause toxicity.
(4) **Diet:** Cruciferous vegetables, like cabbage, increase, whereas bioflavonoids decrease metabolism.

(5) **Alcohol:** Acute ingestion decreases the enzymes thus delaying the metabolism. The result is opposite in chronic alcoholism. Thus chronic ingestion can cause failure of therapy.

(6) **Environmental factors:** Heavy cigarette smoking, exposure to insecticide vapours increase metabolism.

(7) **Malnutrition:** This probably decreases the biotransformation.

(8) **Time of day:** Metabolism of drugs may depend on the time of day when the drug is administered. Examples of drugs which follow these chronopharmacological changes in biotransformation include ampicillin, carbamazepine, costicosteroids, cyclosporine, digoxin, indomethacin, lithium, theophylline.

(9) **Enzyme induction:** Certain drugs are capable of increasing the enzyme content (enzyme inducers) and can alter the therapeutic response due to increased metabolism of drugs administered concurrently. Examples of enzyme inducers include barbiturates, carbamazepine, griseofulvin, phenytoin, phenobarbitone, primidone, rifampicin, sulfinpyrazone, chronic alcohol and tobacco smoke.

Importance:

(*a*) Drug interactions can occur, *e.g.*, failure of oral contraceptive therapy, loss of anticoagulant control due to increased metabolism of these drugs.

(*b*) Disease may result, *e.g.*, antiepileptics can increase the breakdown of vitamin D_3 and produce vitamin D deficiency state (osteomalacia).

(*c*) There can be tolerance to drug therapy, *e.g.*, autoinduction of antiepileptics.

(*d*) There can be variability in therapeutic response; especially alcoholism and smoking can be unrecognised causes of therapy failure.

(*e*) Drug toxicity can occur, *e.g.*, paracetamol toxicity is more common in alcoholism due to enzyme induction.

Benefits: Phenobarbitone is used in hyperbilirubinaemia of newborn to increase the metabolism of bilirubin by enzyme induction and thereby decrease the jaundice.

(10) **Enzyme inhibition:** Certain drugs have the ability to decrease the enzyme content (enzyme inhibitors) and consequently cause toxicity due to accumulation of drugs because of decreased metabolism. For example,

(*i*) Cimetidine increases the levels of propranolol, theophylline, warfarin and phenytoin.

(*ii*) Erythromycin increases the levels of theophylline, warfarin, carbamazepine and methylprednisolone.

Some drugs act through enzyme inhibition (Table 3.7) but they do not affect metabolism.

(11) **Genetic influences:** Genetic variations can affect drug metabolism in a number of drugs.

(*a*) Polymorphic n-acetyltransferases metabolise INH, hydralazine and dapsone. Slow acetylators may show toxicity due to delay in metabolism of these drugs.

Table 3.7 Drugs acting through enzyme inhibition

Drug	Enzyme inhibited	Therapeutic use
1. Acetazolamide	Carbonic anhydrase	Glaucoma
2. Allopurinol	Xanthine oxidase	Gout
3. Moclobemide	Monoamine oxidase-A	Depression
4. Selegiline	Monoamine oxidase-B	Parkinsonism
5. Benserazide	DOPA decarboxylase	Parkinsonism
6. Enalapril	Angiotensin-converting enzyme	Hypertension
7. Disulfiram	Aldehyde dehydrogenase	Alcoholism
8. Diclofenac	Cyclo-oxygenase	Rheumatoid arthritis

(*b*) Abnormal plasma cholinesterase will fail to metabolise succinylcholine thus resulting in prolonged apnoea.

(*c*) Deficiency of glucose-6-phosphate dehydrogenase can cause haemolytic anaemia on exposure to certain drugs like primaquine, dapsone and nitrofurantoin.

(12) **Interethnic differences:** Different races and individuals may show variant response in biotransformation of drugs.

(13) **Thyroid disorders:** Hyperthyroidism increases and hypothyroidism decreases metabolism.

Prodrugs

This term is used to describe compounds that require metabolic transformation after administration to produce the desired pharmacologically active compound. A prodrug may be designed preferentially for the following reasons:

(*a*) **Solubility:** May be designed to possess solubility advantage over the active drug, enabling the use of specifically desired DF and route of administration.

(*b*) **Absorption:** May be either made more water-soluble or lipid-soluble to facilitate absorption via the intended route of administration.

(*c*) **Biostability:** Design of the product may protect the drug during its transport in the body and use of the product could result in site-specific action of greater potency.

(*d*) **Prolonged release:** May provide prolonged drug release and extended therapeutic activity. Examples of prodrugs and their active compounds (in addition to those mentioned earlier in this chapter) include:

- Bacampicillin → ampicillin
- Ramipril → ramiprilat
- Dipivefrin → adrenaline
- Carfecillin → carbenicillin

D. EXCRETION OF DRUGS

Kidney is the main organ of excretion of drugs. Excretion of a drug involves the removal of unchanged drug or its biotransformed product/metabolite from the body. Drugs are also excreted in the lungs, saliva, sweat, bile, intestines, hair, skin and milk.

(1) Renal Excretion

Three processes—glomerular filtration, tubular reabsorption and active tubular secretion—control the urinary elimination of drugs.

(*a*) **Glomerular filtration:** Any drug with molecular weight <20000 can be filtered through the glomerulus. As plasma proteins are almost completely retained within the bloodstream, bound drugs are not subject to filtration.

(*b*) **Tubular reabsorption:** Tubular membrane is permeable to lipid-soluble, non-ionized form of the drug. Compounds that are charged and poorly lipid soluble are poorly reabsorbed.

(*c*) **Active tubular secretion:** This is the active transport process whereby the drug is transported against a concentration gradient from blood capillaries across the tubular membrane into the renal tubule. Competitive secretory transport mechanisms also have a role to play here. Probenecid actively competes with penicillin G and inhibits its tubular secretion thus increasing its stay in the system. Examples of drugs excreted by tubular secretion include:

(*i*) Acidic drugs like acetazolamide, penicillin G, furosemide, indomethacin, phenylbutazone, probenecid, salicylic acid, thiazides.

(*ii*) Basic drugs like dopamine, quinine, quaternery ammonium compounds.

Urinary pH and Renal Excretion

Urinary pH affects the excretion of drugs. Acidic drugs are eliminated faster in alkaline urine. Basic drugs are excreted faster in acidic urine (Table 3.8). Some agents as well as drugs can cause changes in urinary pH and thus affect excretion of other drugs. This effect can be used therapeutically in case of overdose of drugs. Acidification and alkalinisation of urine with certain substances (Table 3.9) can help in rapid elimination of drugs during toxic accumulation.

Table 3.8 Acidic and basic drugs

(*i*) Acidic drugs	
	Acetyl salicylic acid, barbiturates, nitrofurantoin, phenylbutazone, sulfonamides, benzyl penicillin, dicoumarol, phenytoin, theophylline, tolbutamide, warfarin, cloxacillin, naproxen, probenecid, sulfinpyrazone.
(*ii*) Basic drugs	
	Amphetamine, atropine, chloroquine, codeine, morphine, quinidine, procaine, chlordiazepoxide, cocaine, quinine, reserpine, amitriptyline, chlorpromazine, diazepam, imipramine, lignocaine, nifedipine, propranolol, verapamil.

Table 3.9 Agents causing change in urinary pH

(*i*) Agents that increase the pH	
	Acetohexamide, amiloride, amphotericin B, sodium or potassium citrate, niacinamide, sodium bicarbonate, triamterene.
(*ii*) Agents that decrease the pH	
	Ammonium chloride, ascorbic acid, corticotrophin, glucose, diazoxide, methenamine mandelate, metolazone, niacin, sucrose.

(2) Biliary Excretion

A number of drugs are removed from the blood for excretion into the bile and eventually the faeces. In general, these drugs have molecular weights larger than 300. The transport process is an active one in which the dissolved drug is transferred from the plasma to the bile against the concentration gradient.

Examples of drugs excreted in bile: Chloramphenicol, diazepam, doxycycline, ceftriaxone, nafcillin, oxacillin, piperacillin, cefoperazone, indomethacin, streptomycin, quinine.

Drugs like colchicine, INH, phenytoin, phenolphthalein, salicylates, tricylic antidepressants may be reabsorbed into the intestines (enterohepatic cycling/circulation) thus prolonging the duration of action of the drug.

(3) Other Routes of Excretion

These include the lungs, sweat, saliva and the breast milk. Drugs excreted by these routes include:

(*i*) **Lungs:** Anaesthetic gases, ammonium chloride, ethanol, iodides, sodium carbonate.

Table 3.10 Drugs excreted unchanged in urine

Acetazolamide	Chlorothiazide	Penicillin G	Amikacin
Amoxycillin	Cimetidine	Tobramycin	Flucytocine
Ampicillin	Dexamethasone	Vancomycin	Kanamycin
Carbenicillin	Digoxin	Amantadine	Spectinomycin
Cefaclor	Ethambutol	Methotrexate	Trimethoprim
Cefadroxil	Furosemide	Pyridostigmine	Metformin
Cephalexin	Gentamicin	Atenolol	Amiloride

Table 3.11 Drugs appearing in breast milk

Ampicillin	Anticoagulants	Antihistaminics	Aspirin
Carbamazepine	Chloramphenicol	Corticosteroids	Chlorpromazine
Diazepam	Ergot alkaloids	Erythromycin	Diphenylhydantoin
Quinine	Sex hormones	Tetracyclines	Thyroxine
Rifampicin	Acetazolamide	Chlorothiazide	Penicillin G
Amikacin	Sulfonamides	Theophylline	Tolbutamide .
Lithium	Phenobarbitone	Imipramine	Aminoglycosides
Methotrexate	Lincomycin	Metronidazole	Oral contraceptives
Penicillin	Phenylbutazone	Propylthiouracil	INH

Table 3.12 Half lives of drugs

(*i*) Very long t½ (days)	Amiodarone (> 25), Auranofin (17–25), Chloroquine (3–10), Furosemide (3), Pentamidine (3), Phenobarbitone (3–4), Pyrimethamine (3), Tamoxifen (4–11), Ethosuximide (2), Fluoxetine (2), Piroxicam (2), Flurazepam (3), Mefloquine (20).
(*ii*) Long t½ (hours)	Alprazolam (12), Amantadine (16), Amitriptyline(21), Carbamazepine (15), Doxycycline (16), Haloperidol (18), Lisinopril (12), Minocycline (16), Naproxen (14), Quinine (11), Sotalol (12), Trimethoprim (10), Imipramine (3–20).
(*iii*) Short t½ (hours)	Paracetamol (2), Captopril (2.2), Cimetidine (2), Diclofenac (1.1), Erythromycin (1.6), Lovastatin (1.1), Gemfibrozil (l.l), Ibuprofen (2), Prazosin (2.9), Pancuronium (2.3), Neostigmine (1.3), Naloxone (1.1), Nifedipine (1.8), Zidovudine (1.1), Dexamethasone (3).
(*iv*) Very short t½ (min.)	Human insulin (4), Adrenaline (3-10), Dobutamine (2), Dopexamine (7), Esmolol (8).
(*v*) Ultra short t½ (sec.)	Adenosine (1–3).

(*ii*) **Sweat:** Sodium chloride, sulfonamides, urea, thiamine, p-aminohippuric acid.

(*iii*) **Saliva:** Propranolol, methylprednisolone, metoprolol, lithium, amphetamine, lidocaine, paracetamol, trimethoprim, ethosuximide, INH.

(*iv*) **Breast milk:** Many drugs appear in milk although all may not cause harm to the breast-fed infant (Table 3.11).

Half-Life (t½)

Definition: This is the time taken by a drug to reach half the peak value previously attained.

Implications

(*a*) Knowledge of t½ may assist in the dosing of the drug. Drugs with short t½ are in general administered more frequently than the drugs with long t½.

(*b*) Under normal healthy conditions, t½ of drug remains the same. There is a change in t½ only when the efficiency of the eliminatory mechanism fails (*e.g.*, renal failure).

(*c*) Pharmacological effect may last longer than the t½, if the metabolite is active (*e.g.*, propranolol) or in case of post-antibiotic effect (*e.g.*, ciprofloxacin).

(*d*) Drugs with similar half lives can be combined, *e.g.*, trimethoprim and sulfamethoxazole.

Kinetics of Elimination

(1) **First order (exponential) kinetics:** Rate of elimination of drugs is directly proportional to drug concentration. Thus constant fraction of the drug/metabolite is eliminated per unit time. Most of the drugs follow this pattern.

(2) **Zero order (linear) kinetics:** Rate of elimination of drugs remains constant irrespective of drug concentration. This constant amount of the drug is eliminated per unit time. Alcohol follows this pattern.

(3) **Michaelis-Menten kinetics:** As plasma concentration increases, the clearance is decreased and half-life gets longer. This is due to saturation of enzymes metabolizing the drug. Few drugs like phenytoin, theophylline, warfarin and tolbutamide follow this pattern. The elimination is exponential initially followed by linear later.

❍❍❍

FIND OUT

1. What is Fick's law of diffusion?
2. What do you mean by relative bioavailability?
3. Which co-factor is required for microsomal oxidation/reduction?
4 What is one compartment model of pharmacokinetics?
5. Which drugs are given with or after food
   (a) to reduce gastric adverse effects, and
   (b) to increase absorption?

INSTRUCTION QUERIES

A doctor often asks the patient to take the drugs with reference to food. What does It mean when he says:

1. Before meals
2. Empty stomach
3. Empty stomach preferably
4. With or after food
5. With or without food

4

Pharmacodynamics

LEARNING OBJECTIVES

- Mechanisms of drug action
- Therapeutic index and its importance
- Factors modifying drug dose and effects
- Methods to prolong drug action

Pharmacodynamics is 'what the drug does to the body'—drug effects and the mechanism of drug action.

Mechanism of Drug Action

- Drugs may act in two broad ways: Via receptors or without the interaction of receptors.
- Non-receptor mechanism may be osmosis, chelation, enzymatic interactions, interference with cellular functions, etc.

Receptors

These are specialised target macromolecules present in the cells or on the cell surface, that bind a drug and mediate its pharmacological action.

Terms Associated with Drug-Receptor Interactions

- **Affinity:** Ability of the drug to bind to the receptor.
- **Intrinsic activity (efficacy):** Ability of the drug to initiate a response.
- **Agonist:** Drug which has affinity and intrinsic activity of 1; binds to the receptor and elicits a response, *e.g.,* morphine.
- **Antagonist:** Drug which has affinity but no intrinsic activity; binds to the receptor and blocks it without producing a pharmacological action; this prevents agonist from binding to the receptor thus giving rise to responses opposite to that of the agonist, *e.g.,* naloxone.
- **Partial agonist:** Drug which has affinity and submaximal intrinsic activity; binds to the receptor, blocks it but causes less response than a full agonist, *e.g.,* buprenorphine, pindolol.
- **Inverse agonist:** Drug which has affinity and intrinsic activity to produce a response opposite to that of an agonist, *e.g.,* β-carbolines.
- **Downregulation of receptors:** Decrease in the count of receptors when tissues are continuously exposed to an agonist, *e.g.,* use of salbutamol (β_2 agonist).
- **Upregulation of receptors:** Increase in the count of receptors when tissues are continuously

exposed to an antagonist, *e.g.,* use of propranolol (β antagonist).

Autoreceptors vs Heteroreceptors

(*a*) **Autoreceptors:**

- Presynaptic receptors that respond to the primary transmitter substance released by the nerve endings.
- Usually inhibitory but many cholinergic fibres especially somatic motor fibres have excitatory nicotinic autoreceptors.

(*b*) **Heteroreceptors:**

- Regulatory receptors on nerve terminals that respond to many other substances.
- May be activated by substances released from other nerve terminals that synapse with the nerve endings, *e.g.,* vagal fibres in myocardium synapse on sympathetic norepinephrine nerve terminals and inhibit norepinephrine release.

Physiological Receptors (Table 4.1)

- Most number of drug receptors are physiological receptors expressed on the cell surfaces.
- They have two major functions — ligand binding and message propagation (intracellular signalling).

Table 4.1 Physiological receptors

Family	Functional group	Physiological ligands	Effectors and transducers	Drugs
I. G-protein coupled receptors	(i) β-adrenergic receptors	Noradrenaline, Adrenaline Dopamine	Adenylyl cyclase Gs protein	Propranolol Dobutamine
	(ii) Muscarinic cholinergic receptors	Acetylcholine	Adenylyl cyclase Ion channels, Gi/Gq proteins Phospholipase C	Atropine
	(iii) Eicosanoid receptors	Prostaglandins Leukotrienes Thromboxanes	G proteins (Gs, Gi, Gq)	Montelukast Misoprostol
II. Ion channels	(i) Ligand gated	GABA, serotonin Acetylcholine (M_2)	Na^+, K^+, Cl^-, Ca^{++}	Gabapentin Nicotine
	(ii) Voltage gated	—	Na^+, K^+, Ca^{++}	Lignocaine verapamil
III. Intracellular enzymes	Soluble guanylyl cyclase	Nitric oxide, Ca^{++}	Cyclic GMP	Nitrates
IV. Nuclear receptors	(i) Peroxisome proliferator activated receptor (PPAR γ)	PPAR γ	—	Pioglitazone
	(ii) Thyroid hormone receptors	Thyroxine	—	Thyroxine
	(iii) Steroid receptors	Testosterone Oestrogen	—	Androgens Oestrogens
V. Transmembrane enzymes	(i) Receptor tyrosine kinases	Insulin, Growth factors	SH_2 domain	Herceptin Imatinib
	(ii) Membrane guanylyl cyclase	Natriuretic peptides	Cyclic GMP	Nesiritide
VI. Transmembrane non-enzymes	Cytokine receptors	Interleukins	Janus kinase	Anakinra

- Thus there are two functional domains existing within a receptor—ligand-binding domain and effector domain.
- The regulatory actions of a receptor may be exerted directly on its cellular target, on effector protein or on intermediary cellular signaling molecules (transducers). This chain is termed as 'receptor-effector system' or 'signal transduction pathway'.
- Often, the proximal cellular effector protein is not the final physiological target. It is an enzyme, ion channel or a transport protein, that creates, moves or degrades a small molecule (inositol 1, 4, 5-triphosphate, nitric oxide or a cyclic nucleotide) or ion (ca^{++}). These are termed as 'second messengers'.
- Second messengers either diffuse in the proximity of their synthesis and interact with selective targets, or convey information to a variety of targets that may integrate multiple signals.
- Physiological receptors have capacity to amplify a physiological signal. Neurotransmitters, hormones and other extracellular ligands are often present at the ligands binding domain of a receptor in nanomolar to micromolar concentrations. However, the effector domain contains enzymes that amplify the intended signal. These signalling systems are good targets for drugs.
- Six major families of physiological receptors are known. Their physiological ligands, signal transduction systems and drugs affecting these systems are outlined in Table 4.1.

Non-Receptor Mechanisms

(*a*) **Osmosis:**
- Magnesium sulphate produces a purgative effect due to osmosis.
- Mannitol raises the osmotic tension of renal tubular fluid and prevents reabsorption of tubular fluid to act as a diuretic.

(*b*) **Chemical interactions:**
- Aluminium hydroxide chemically neutralises the gastric acid to act as an antacid.
- Chelating agents like EDTA and BAL interact with metals to form water-soluble complexes easily eliminated in urine.

(*c*) **Enzymatic modifications:**
- Anticholinesterases act by inhibiting acetylcholinesterase.
- Enalapril, ramipril act by inhibiting angiotensin-converting enzyme.

(*d*) **Antibacterial actions:**
- Penicillin acts by inhibiting cell wall synthesis of bacteria.
- Streptomycin acts by inhibiting protein synthesis.

(*e*) **Physical mass:**
- Agar agar produces a purgative effect because of swelling in presence of water which increases its size.

(*f*) **Electrical charge:**
- Heparin produces anticoagulant effect by binding to positively charged antithrombin III because of its negative charge.

(*g*) **Other mechanisms:**
- Anaesthetic gases cause depression of many neurons in the brain by altering excitability of the neuronal membrane.
- Radioactive isotopes act by emitting ionising radiations.
- Liquid paraffin coats the faecal matter and produces laxative effect.

Factors Modifying Drug Dose and Effects

(1) **Age:** Lesser dose should be given to children than for adults due to immaturity of renal functions and poor development of enzymes needed for metabolism of drugs. Various formulae are available for calculating the doses in children (Refer to the chapter on 'Drug use at Extremes of Age').

(2) **Body weight and surface area:** Body weight has a definite influence on the drug concentration at the site of action. Charts are available to calculate dose according to body surface area.

(3) **Sex:** Females are more susceptible to the effects of certain drugs. Special care is required when drugs are administered during menstruation, pregnancy and lactation.

(4) **Diet and environment:** Certain drugs are given on empty stomach as food decreases

bioavailability. Time of day can influence the drug action. Sedative dose required for inducing action is less at night than during the day. Smoking and alcoholism can adversely modify drug effect.

(5) **Route of administration:** Rate of drug absorption differs according to the route. IM is usually faster than the oral with a few exceptions (lorazepam, diazepam). Dose also varies according to the route. IV dose may be smaller than oral dose.

(6) **Pharmacogenetics:** Inherited enzyme deficiencies may influence drug action. Primaquine produces haemolysis in individuals with G-6-PD deficiency. Rate of acetylation of INH, hydralazine, procainamide is controlled by genes. People with atypical pseudocholinesterase may develop apnoea after succinylcholine.

(7) **Psychological or emotional factors:** Psychological status may influence the drug effect and patient response. Psychotics need a larger dose of drugs for quietening effect as compared to a normal person. Placebos (dummy drugs) are sometimes useful to please the patient.

(8) **Metabolic factors:** Changes in body temperature, electrolyte balance and acid-base status can modify drug effects. Salicylates lower body temperature only in fever. Biguanides decrease blood sugar only in diabetics.

(9) **Pathological state:** Liver failure, kidney failure, hyperthyroidism, CHF, cirrhosis can influence the drug effects. Aminoglycosides can cause toxicity in renal insufficiency. Larger doses of opioids may be required in hyperthyroidism.

(10) **Cumulation:** Drugs which are excreted slowly (digitalis, emetine) can accumulate in the body on prolonged use and cause toxic effects.

(11) **Drug interactions:** Two or more drugs, if given together, can cause a variety of responses—additive, antagonistic or toxic. Two drugs, if mixed in a syringe, may precipitate one of them causing failure of therapy.

(*a*) ***Drug antagonism:*** Two drugs act on the same physiological system and produce opposite effects. Antagonism can be of following types:

(*i*) *Chemical:* Occurs as a result of chemical interaction between two drugs, *e.g.,* BAL and arsenic, acid and alkalies.

(ii) *Physiological:* Drug and the antagonist act at different receptors to produce opposite effects, *e.g.,* adrenaline and histamine.

(*iii*) *Competitive or reversible or surmountable:* Two drugs compete for the same receptors, drug having greater concentration at the receptor produces the effect, *e.g.,* acetylcholine and atropine. A competitive antagonist shifts the dose response curve to the right (Fig. 4.1).

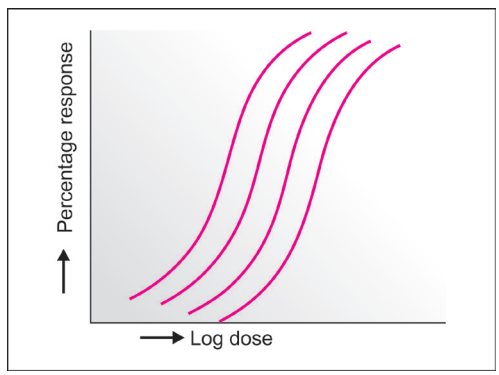

Fig. 4.1 Competitive antagonism (DRC with agonist in presence of competitive antagonist)

(*iv*) *Non-competitive or irreversible or unsurmountable:* Occurs due to inactivation of the receptor by the antagonist, *e.g.,* acetylcholine and decamethonium at the neuromuscular junction. In non-competitive antagonism, although the agonist curve will shift to the right, the slope will be reduced and the maximal response will diminish (Fig. 4.2).

(*v*) *Functional:* Interaction of two agonists that act independently of each other but happen to cause opposite effects, *e.g.,* adrenaline and acetylcholine.

(*b*) ***Drug synergism:*** Total effect produced by two drugs is greater than the sum of individual effects, *e.g.,* aspirin and codeine, trimethoprim and sulfamethoxazole.

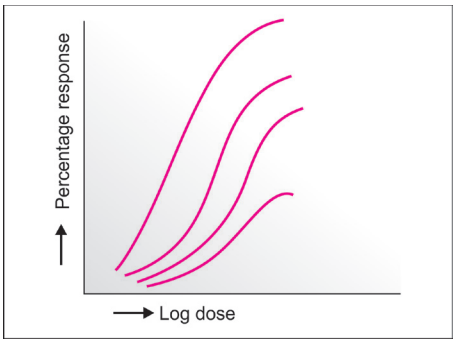

Fig. 4.2 Non-competitive antagonism (DRC with agonist in presence of non-competitive antagonist)

(*c*) ***Drug additive effect:*** Total pharmacological effect of two drugs is equal to the sum of their individual effects, *e.g.,* ephedrine and aminophylline in asthma.

(12) **Drug tolerance:** When an unusually large dose of a drug is required to elicit a response originally produced by the therapeutic dose, the phenomenon is termed as tolerance. It can be natural and acquired.

(*a*) ***Natural:*** Seen among various human races.

(*b*) ***Acquired:*** Develops only on repeated administration of drug:

(*i*) *Tissue tolerance:* Development of tolerance confined to certain effects or to certain systems, *e.g.,* morphine develops tolerance for euphoria, not for miosis or constipation.

(*ii*) *Cross tolerance:* Individual developing tolerance to a drug belonging to one group, shows tolerance to other drugs belonging to same group, *e.g.,* individual tolerant to glyceryl trinitrate is also tolerant to isosorbide dinitrate.

Tachyphylaxis: This is an acute type of tolerance which occurs rapidly after repeated administration of the drug at short intervals, *e.g.,* acute tolerance to ephedrine in asthma treatment, if used repeatedly rapidly.

(13) **Drug dependence:** Repeated administration of certain drugs can cause 'habit' and dependence. Acute withdrawal syndrome can result, if the patient is not able to get the dose of the drug in case of chronic ingestion of certain drugs of abuse, *e.g.,* narcotic analgesics like morphine.

Methods of Prolonging Drug Action

The drug action can be prolonged by:

(*a*) Delaying the absorption of drug.
(*b*) Inhibiting or decreasing drug metabolism.
(*c*) Decreasing renal excretion.
(*d*) Increasing protein binding.

Delaying the absorption of the drug: Absorption, can be decreased by the following methods:

(1) Taking the drug on full stomach (with some exceptions like cefuroxime axetil or cefpodoxime proxetil) or in enteric coated forms.
(2) Reducing the solubility of the drug; this can be achieved by combining the drug with a compound having poor water solubility, *e.g.,* combining penicillin with procaine.
(3) Use of vasoconstrictors, *e.g.,* adrenaline used in combination with lignocaine.
(4) Administration of drug in oily solution, *e.g.,* adrenaline in oil.
(5) Combination of the drug with a protein, *e.g.,* insulin in combination with protamine.
(6) Esterification of the drug, *e.g.,* long-acting esters of sex hormones.
(7) Implantation of drug pellets, *e.g.,* desoxy corticosterone actate (DOCA) pellets.
(8) Use of osmotic drug delivery systems.
(9) Use of transdermal drug delivery systems.

Inhibiting or decreasing drug metabolism: Inactivation of drugs by microsomal enzymes of liver can be decreased by certain compounds, *e.g.,* inhibition of monoamine oxidase enzyme by drugs like moclobemide, selegiline and others.

Decreasing renal excretion: Excretion of certain drugs can be delayed by the use of drugs, *e.g.,* excretion of penicillins and cephalosporins can be delayed by probenecid.

Increasing protein binding: Highly protein bound drugs can have prolonged action, *e.g.,* suramin used

in trypanosomiasis is extensively protein bound and has long duration of action.

Therapeutic Index

It is defined as the ratio of median lethal dose to median effective dose.

$$\text{Therapeutic Index (TI)} = \frac{\text{LD 50}}{\text{ED 50}}$$

- LD50 (median lethal dose) is the dose which kills 50% of animals tested belonging to the same species and strain.
- ED50 (median effective dose) is the dose which produces desired response in 50% of animal population tested.

Significance of TI

- It is a measure of drug's safety: A large TI indicates that there is a wide margin between toxic and effective doses.
- It gives some indication of the probability of facing the adverse effects in clinical practice, *e.g.,* lithium with TI of 2 can cause toxicity, if the dose is doubled.

Limitations of TI

- Values of TI are based on animal data and may not be entirely reproducible in humans.
- ED50 testing in animals depends on what measure of effectiveness is used, *e.g.,* ED50 for acetylsalicylic acid for pain would be lower than ED50 for inflammation.
- LD50 is not a comparable guide to assess toxicity in humans.

Examples of drugs:

- High TI: Penicillin, haloperidol, vitamins.
- Low TI: Digoxin, lithium, antiepileptics, cyclo-sporine, aminoglycosides, warfarin, theophylline, lignocaine.

Modification of TI

A more realistic estimate of drug safety can be achieved by comparing the lowest dose that produces toxicity (*e.g.,* LD1) and the highest dose that produces maximal effect (*e.g.,* ED 99). A ratio less than 1 will mean that a dose effective in 99% of population will be lethal in more than 1% of the individuals taking that dose.

Protective Index

It is defined as the ratio of median effective dose (undesirable effects) to median effective dose (therapeutic response).

$$\text{Protective Index (PI)} = \frac{\text{ED50 (undesirable side effects)}}{\text{ED50 (therapeutic response)}}$$

Consider the use of phenobarbitone where sedation and temporary neurological impairment is commonly seen in therapeutic doses. There are other antiepileptics where these adverse effects may be seen only in higher dose, or not at all. A good PI for an antiepileptic would, therefore, be

$$\frac{\text{ED50 (neurological impairment)}}{\text{ED50 (seizure protection)}}$$

An antiepileptic with PI of 5 would be better than PI of 2.

Placebos

- The word 'Placebo' in Latin means 'I please'.
- A placebo preparation is usually a pharmacologically inactive substance like starch or glucose.
- Used for two purposes:
  - (*a*) As a control in scientific evaluation of drugs (clinical trials).
  - (*b*) To benefit or please a patient not by any pharmacological actions, but by psychological means; often used in the treatment of certain diseases where the psychic element is suspected to be responsible for subjective symptoms.
- **Ideal placebo:** When administered for its therapeutic effects, the placebo preparation must appear relevant to the illness, be harmless and should preferably conform to the patient's expectations; to be very effective, the 'potency' of the preparation must be shown by some signs such as strong taste, a colourful capsule (ideally red, yellow or brown) or a tablet of odd shape.
- Placebos can cause adverse subjective reactions like drowsiness, fatigue, headache, dryness of mouth, insomnia, constipation and a 'drugged feeling'.

- Placebo effect can be modified by:
  (*a*) Personality of the physician: Doctor's reassurance and optimistic outlook can achieve better results.
  (*b*) Personality of the patient: Patients who listen with care and faith take these 'drugs' regularly and talk of relief after taking placebos: 'Placebo reactors'.
  (*c*) Form of administration: Greatest placebo effect is achieved by injections (80%); liquids and tablets are less effective.

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FIND OUT

1. What is the difference between the 'effect' and the 'action'?
2. What do you understand by the 'potency" of a drug?
3. What is 'biophase'?
4. What is EC50?
5. What do the terms therapeutic threshold' and therapeutic ceiling' stand for?

5

Chronopharmacology

LEARNING OBJECTIVES

- Basics of circadian rhythm
- Chronotherapeutic drug delivery systems
- Drugs undergoing chronokinetics

- Nearly all functions of the body, including those influencing PK parameters such as drug absorption, distribution, metabolism and renal elimination, show significant daily variations.
- These include liver metabolism, hepatic blood flow and the first-pass effect; glomerular filtration, renal plasma flow and urine volume and pH; BP, HR and organ perfusion rates; acid secretion in GIT and gastric emptying time.
- The onset and symptoms of diseases such as asthma attacks, coronary infarction, angina pectoris, stroke and ventricular tachycardia are circadian phase dependent.
- In humans, variations during the 24 h day in PK have been shown for cardioactive drugs (propranolol, nifedipine, verapamil, enalapril, isosorbide 5-mononitrate and digoxin), anti-asthmatics (theophylline and terbutaline), anticancer drugs, psychotropics, analgesics, local anaesthetics, antibiotics, and others.
- Many drugs have been shown to display significant variations in their effects throughout the day even after chronic application or constant infusion.
- There is clear evidence that even dose/concentration-response relationships can be significantly modified by the time of day.
- Thus, circadian time has to be taken into account as an important variable influencing a drug's PK and its effects or adverse-effects.
- There is convincing scientific work to indicate that more attention should be given to the timing of drug administration.
- Most prescribers are currently more concerned with "what" to prescribe rather than "when" to prescribe.

Terminology

- Chronobiology is the science of biological rhythms (biological clock).
- The branch dealing with the pharmacological aspects of chronobiology is termed Chronopharmacology. It is the science dealing with

the optimization of drug effects and the minimization of adverse effects by timing the drugs in relation to the biological rhythm. Thus, if drugs are prescribed keeping in mind our body clock, they can prove more beneficial and cause minimal side effects.

- Chronergy is rhythmic changes of both desired (effectiveness) and undesired (toxicity, tolerance) effects on the organism as a whole. On a 24-hour scale, there are peaks and troughs of physiological variables that are not randomly distributed, but controlled by biological clocks.
- Chronokinetics is the study of absorption, distribution, metabolism and excretion of drug according to the time of day, menstrual cycle or year.
- Chronesthesy is rhythmic changes in susceptibility or sensitivity of a target system to a drug, which cannot be explained by chronokinetic changes. In humans, target can be skin, bronchial tree, stomach.

Chronotherapeutic Drug Delivery Systems

- Controlled release formulations: Rate-controlled release, delayed-release and pulsed-release formulations.
- Delayed-release formulations include time-controlled release and site-specific dosage forms.
- When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms.
- By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced.
- Saturable first-pass metabolism and tolerance development can also be avoided.
- Various technologies to develop time-controlled peroral drug delivery systems have been extensively studied in recent decades.

(a) Press-coated systems:

- Delayed-release and intermittent-release formulations can be achieved by press-coating.
- Press-coating or compression coating, is relatively simple and cheap and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions.

(b) Enteric-coated systems:

- Enteric coatings traditionally used to prevent the release of a drug in the stomach are pH-sensitive and drug is released when pH is raised above 5 in the intestinal fluid.
- Due to the unpredictability of gastric resistance, such systems cannot be the first choice when a time-controlled release is required.
- In the treatment of nocturnal asthma, salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above 6 has been successfully used.
- The system contains a core which is film coated with two polymers, first with HPMC and then with a gastroresistant polymer (Fig. 5.1).

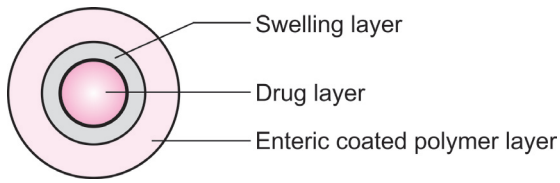

Fig. 5.1 Enteric-coated system

(c) Time-controlled explosion systems (TES):

- These have been developed for both single and multiple unit dosage forms.
- The core contains the drug, an inert osmotic agent and suitable disintegrates.
- Individual units can be coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core.

- As water reaches the core, osmotic pressure is built up.
- The core ultimately explodes, with immediate release of the drug.

(d) Sigmoidal release system (SRS):

- Pellet-type multiple unit preparation containing an osmotically active organic acid coated with insoluble polymer to achieve different lag-times.
- By applying different coating thicknesses, lag times in vivo of up to 5 hours can be achieved.

(e) The pulsatile drug delivery system:

- This is a system where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states.
- No drug is released from the device within this lag time.
- This delivery system is suitable in cases where drugs including proteins and peptides undergo great metabolic degradation.
- Chances of drug resistance and tolerance are less because the desired concentration of the drug is available only at a certain time point.

  Advantages
  - Less inter- and intrasubject variability
  - Improved bioavailability
  - Reduced adverse effects and improved tolerability
  - Limited risk of local irritation
  - Improved stability
  - Improved patient compliance
  - Achieves a unique release pattern

  Disadvantages
  - Proportionally higher need for excipients
  - Large number of process variables
  - Multiple formulation steps
  - Higher cost of production
  - Need of advanced technology

(f) Pulsinocapõ delivery system:

- This releases drug contents at a predetermined time or at a specific site within the gastrointestinal tract.
- Each capsule is composed of a water insoluble body and a water-soluble cap, and also contains the drug dose which is sealed with a hydrogel plug.
- At a predetermined time after ingestion, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon.
- The dimension of the plug and its position in the capsule can be varied and the system delivers drug at exactly the programmed time, 1 to 10 hours after drug administration, to various regions of the gut.

(g) Controlled onset extended-release (COER-24) osmotic system (for verapamil):

- This formulation is tailored to the circadian rhythm of BP and HR to better cover early morning symptoms of cardiovascular diseases.
- Around the device, which consists of a drug layer and a push layer, are two membranes.
- The first is a semipermeable insoluble membrane while the second is a release delaying hydrophilic polymer coat.
- Gastrointestinal fluid penetrates the semipermeable membrane, and as it enters the drug layer and push layer via the hydrated coat (within 4 to 5 hours), the push layer expands, pressing against the drug layer and causing drug release at a constant rate for 18 hours.
- If taken at bedtime, the system provides optimal drug concentration when the patient wakes up and during daytime.

Chronopharmacokinetics

Why study?

- PK-PD vary with time.
- Gastric motility is double in daytime than in night.
- Plasma protein concentrations are higher in day than in night.

- Hepatic blood flow has been shown to be greatest at 8 am and metabolism to be reduced during the night
- Symptoms of certain diseases are circadian phase dependent, *e.g.,* nocturnal asthma, angina pectoris, MI, ulcer diseases.
- Drug toxicity can be avoided/minimized by administering at a particular time

Absorption

- Depends on pH, gastric emptying, motility and gastrointestinal blood flow.
- Lipophilic drugs are better absorbed in morning because of faster gastric emptying time and a higher GI perfusion in the morning.
- Valproic acid, indomethacin, ketoprofen are better absorbed in the morning.
- Skin penetration of lidocaine and prilocaine is better in evening.

Distribution

- Blood flow depends on several regulatory factors known to be circadian time dependent with a predominant diurnal effect of the sympathetic system.
- Plasma concentrations of albumin and alpha 1 glycoprotein are circadian time dependent: Show peak around noon.
- Drugs bound to plasma proteins like valproic acid, carbamazepine, diazepam, prednisolone, etc. show increase in free fraction at night.

Metabolism

- Depends on liver enzyme activity and hepatic blood flow.
- High extraction ratio: Metabolism depends on blood flow.
- Low extraction ratio: Metabolism depends on enzyme activity.
- Hepatic blood flow high in morning.
- Metabolism reduces in night.

Elimination

Renal physiological functions such as glomerular filtration, renal blood flow, urinary pH, and tubular resorption show a circadian time-dependent difference with higher values during daytime.

Chronopharmacodynamics

Circadian rhythm has been found for receptor number, receptor conformation and second messengers.

Drugs undergoing chronokinetics

1. *Antibiotics:*

- Aminoglycosides: Gentamicin, tobramycin, amikacin
- Renal toxicity of aminoglycosides can be reduced by giving the drug as a single daily injection when patients are active (at daytime / in the activity period).

2. *Anti-inflammatory drugs:* Have greater rates and extents of bioavailability when administered in the morning than evening, *e.g.,* indomethacin, ketoprofen.

3. *Antihypertensive drugs:*

- C_{max} was higher and/or t_{max} shorter after morning than evening dosing of the lipophilic drugs (nifedipine, oral nitrates, propranolol).
- Atenolol is not absorbed rapidly after morning administration.
- ACE inhibitors were found to be safe and effective when administered at bedtime when compared to morning.

4. *Valproic acid:* C_{max} tended to be higher, t_{max} was shorter in the morning than in evening.

5. *Anti-migraine drugs:* Sumatriptan mean peak serum concentration was significantly higher at 7 am than after 7 pm administration.

6. *Anticancer drugs:*

- The activity of dehydropyrimidine dehydrogenase in human mononuclear cells increases by 40% around midnight.
- This enzyme brings about the intracellular catabolism of 5-FU and contributes to improved tolerability of this drug between 12 pm and 4 am.

7. *Antihyperlipidemic drugs:*

- More cholesterol synthesis takes place in the

evening than in the morning with the involvement of the enzyme HMG CoA reductase.

- Statins should be administered in the evening for increased efficacy with the exception of atorvastatin which has got longer half life.

8. ***Opioid analgesics:***

- Stronger analgesic effects were observed when tramadol was given in the evening.
- A recent study reveals maximal analgesic effect of pethidine occurring with the morning dose.

9. ***Heparin:*** Even if given at a constant infusion rate, risk of bleeding is higher at night.

10. ***Topical steroids:*** Anti-inflammatory action is maximum in afternoon.

11. ***Local anesthetics:***

- The duration of local anaesthesia was the longest when amide-type local anaesthetics (lidocaine, ropivacaine, mepivacaine, betoxycaine) were applied around 3 pm.
- The plasma levels of lidocaine were significantly higher in the evening than at any other time of day.

12. ***General anaesthetics*****:**

- The elimination half-life of midazolam was found to be at its shortest at 2 pm and at its longest at 2 am.
- Ketamine, etomidate, propofol, and halogenated agents' action was longer during the night than during the day.

13. ***Antipsychotic drugs:***

- Chlorpromazine would be most effective in producing sedative and antipsychotic effects when administered at midnight and immediately after rising, respectively.
- For haloperidol, administration in the evening would be best for obtaining either a sedative or antipsychotic effect.

Chronotherapeutics

- Refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize the adverse effects.
- The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity.

Chronotherapy is found useful in:

1. Allergic rhinitis
2. Bronchial asthma
3. Peptic ulcer disease
4. Rheumatoid arthritis, osteoarthritis
5. Angina pectoris
6. MI
7. Hypertension, stroke
8. Cancer

Necessity of Chronotherapeutic Approach

- When the "therapeutic window" for a given drug is very narrow.
- When the toxicity of the drug is a factor of dose limitation.
- When the kinetics and or the effects are dependent on the moment of the administration.
- When the effect of the drug can be obtained only by a time-modulated therapeutical modality.

Potential Benefits of Chronotherapeutics

1. ***Pain and inflammation:***

- NSAIDs may be more effective at relieving pain, if they are administered at least 6 hours before the pain reaches its peak.
- The symptoms of rheumatoid arthritis are worse in the morning.
- Osteoarthritis pain less in the morning and more at night.
- NSAIDs effectively relieve pain of RA when given at night, and better results in case of OA are seen when these are given in morning.

2. *Bronchial asthma:*

- The risk of asthmatic attack is almost 70 times higher in patients between 4 and 5 am in the morning, compared with the afternoon.
- Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms.
- Cortisol levels are highest at the time of awakening and lowest in the middle of the night, and histamine concentrations peak at a level that coincides with the greatest degree of bronchoconstriction at 4 am.
- A research finding also reveals that theophylline absorption is slower at night. SR formulation at night increases efficacy.
- Single daily dose of inhaled corticosteroids, when administered at 5.30 pm rather than 8 am, is nearly as effective as four doses a day.
- Single dose oral prednisolone at 3 pm is most effective.

3. *Cancers:*

- The biological rhythms of both healthy and tumour cells may influence their susceptibility to anticancer agents.
- Anticancer drugs (S phase specific) are administered at night-time, because cancer cells divide more at night-time and host cells in morning.
- 6-mercaptopurine and methotrexate are better given in the evening.
- Colorectal cancer: Oxaliplatin is given during daytime and fluorouracil at night.
- Breast cancer: Surgery during later half of the menstrual cycle—more clearance rate than early half.
- Progesterone in the later half inhibits the enzymes responsible for spread of cancer cells.

4. *Allergic rhinitis:*

- Rhinitis—worst in the morning and evening.
- Once-daily, non-sedating antihistaminic before bedtime ideal.
- Morning oral corticosteroid therapy recommended for severe allergic rhinitis.

5. *Peptic ulcer:*

- Maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night.
- H_2 blockers are better given at evening time.

6. *Diabetes mellitus:* Morning hyperglycemia may be observed in patients with diabetes mellitus.

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