Section

I

General Pharmacology

1. Principles of Pharmacology, Evidence-based Medicine and Routes of Drug Administration
2. Pharmacokinetics
3. Pharmacodynamics
4. Adverse Drug Reactions, Pharmacovigilance and Drug Interactions
5. Drug Nomenclature, Drug Development, Drug Regulations, Essential Medicines, Prescriptions and Related Topics

Chapter

1

Principles of Pharmacology, Evidence-based Medicine and Routes of Drug Administration

Competencies

PH1.1 Describe the principles of pharmacology, pharmacotherapeutics and define various terms in pharmacology.

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems. The word pharmacology is derived from the Greek word—**Pharmacon** meaning an active principle and **logos** meaning a discourse.

HISTORICAL ASPECTS

The useful and toxic effects of many plant and animal products were known to man since ancient times. In fact, there has been a quest for drugs and remedies since the existence of mankind itself.

In early days, there was a close relationship between religion and the treatment of diseases. The knowledge of the use of drugs often rested with the priest or holyman. Drugs were thought to be magical in their actions. Several cultures like the Chinese, Greek, Indian, Roman, Persian, European and many others contributed a great deal to the development of medicine in early times. The drug prescriptions included preparations from herbs, plants, animals and minerals. However, written information on remedies used in early times is lacking.

The Indian and the Chinese writings are amongst the oldest written material in medicine. India's earliest pharmacological writings are from the 'Vedas'. Rigveda (3000 BC) has description of some medicines. An ancient Indian physician Charaka, and then, Sushruta and Vagbhata, described many herbal preparations included in **'Ayurveda'** (meaning the science of life). Indians practiced vaccination as early as 550 BC.

'Pen Tsao' the Chinese materia medica was written as early as 1700 BC, and it contained classification of medicinal plants and some preparations of plants, metals and animals.

The Egyptian medical papyri (1600 BC) described several preparations. The largest of them, Ebers Papyrus lists some 800 preparations.

The Greeks studied the toxic effects of various plant extracts. Their contribution to the growth of modern medicine is significant. **Hippocrates** (460–377 BC), a Greek physician, studied the cause of disease and wrote on the ethics of medicine and recommended judicious use of drugs. Galen (130–201 BC), also a Greek physician, practiced in Rome and put forth a doctrine that diseases are due to an imbalance of fluids—blood, phlegm, black bile and yellow bile. He believed that drugs had some properties like warmth, coldness, dryness or humidity and also thought that it is beneficial to use a combination of drugs to obtain these effects.

In the Middle Ages, many herbal gardens were cultivated by the monasteries. **Paracelsus** the **'Grandfather of Pharmacology'** born in Switzerland was the son of a physician. He opined that complicated mixture of drugs

should not be used and also wrote, "all drugs are poisons—it is only the dose which makes a thing a poison." This statement holds good even today.

Though medicine developed simultaneously in several countries, the spread of knowledge was limited because of poorly developed communication across the world. By the beginning of the first century, it was realized that there was a need to standardize the method of obtaining uniform medical preparations.

James Gregory (1735–1821 AD) recommended certain dangerous measures like blood letting, use of emetics and purgatives in the treatment of diseases—such measures were often fatal. He meant to induce other suffering to relieve pain/suffering and this was probably the basis of the word **'allopathy'** meaning 'the other suffering'. This word, still being used for the modern system of medicine, is a misnomer. **Homeopathy** meaning 'similar suffering' was introduced by **Samuel Hahnemann**. The principles of this system include 'like cures like' and 'dilution enhances the potency of drugs'. Various traditional systems of medicine were practiced in different parts of the world like Homeopathy, Ayurveda, Unani, Siddha system and Allopathy.

Thus several systems of medicine were introduced, of which only a few survived. The basic reason for the failure of these systems is that man's concepts about diseases were incorrect and baseless in those days. By the end of the 17th century, the importance of experimentation, observation and scientific methods of study became clear. **Francois Magendie** and **Claude Bernard** popularized the use of animal experiments to understand the effects of drugs. Simultaneous development of other branches of science, viz. botany, zoology, chemistry and physiology helped in the better understanding of pharmacology.

By the nineteenth century, methods for isolation of drugs were developed. **Rudolph Bucheim** (1820–1879) set up the first laboratory in his home at Dorpat Estonia in 1847 exclusively meant for research on drugs. **Oswald Schmiedeberg** (1838–1921), a student of Bucheim, conducted extensive research on drugs, trained 120 students and wrote a medical textbook. He has been called **'Father of Pharmacology'** for his contribution and was the most prominent pharmacologist of the 19th century.

With the growth of science and the development of scientific methods of research, treatment of diseases now relies largely on scientific evidence. Well-designed multicentric trials involving a fair number of participants are required to prove the safety and benefits of a drug in a given condition before it can be used in general population making the modern system **evidence-based medicine** (*see* page 5).

The last century has seen a rapid growth of the subject with several new drugs, new concepts and techniques being introduced. We now know much more about receptors and molecular mechanisms of action of many drugs. Several diseases, which were considered incurable and fatal, can now be completely cured with just a few tablets.

TERMINOLOGY

Drug (*Drogue*—a dry herb in French) is a substance used in the diagnosis, prevention or treatment of a disease. WHO definition, "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug (in Greek Kinesis = movement).

Pharmacodynamics is the study of the effects of the drugs on the body and their mechanisms of action, i.e. what the drug does to the body.

Therapeutics deals with the use of drugs in the prevention and treatment of disease.

Pharmacoeconomics deals with the cost, i.e. economic aspects of drugs used therapeutically.

Pharmacogenetics (and pharmacogenomics) is the science that deals with the study of genetic basis for variation in drug responses (*see* page 51).

Pharmacoepidemiology is the study of both the useful and adverse effects of drugs on large number of people.

Pharmacovigilance is related to the detection, assessment, understanding and prevention of adverse effects of drugs (*see* page 62).

Toxicology deals with the adverse effects of drugs and also the study of poisons, i.e. detection, prevention and treatment of poisoning *(Toxicon = poison in Greek)*.

Chemotherapy is the use of drugs and chemicals for the treatment of infections. The term now also includes the use of chemical compounds to treat malignancies.

Essential medicines are those that satisfy the healthcare needs of majority of the population and should be available at all times in adequate amounts and in the appropriate dosage forms (*see* page 71) as defined by the WHO.

Orphan drugs are drugs to be used for prevention and treatment of rare diseases.

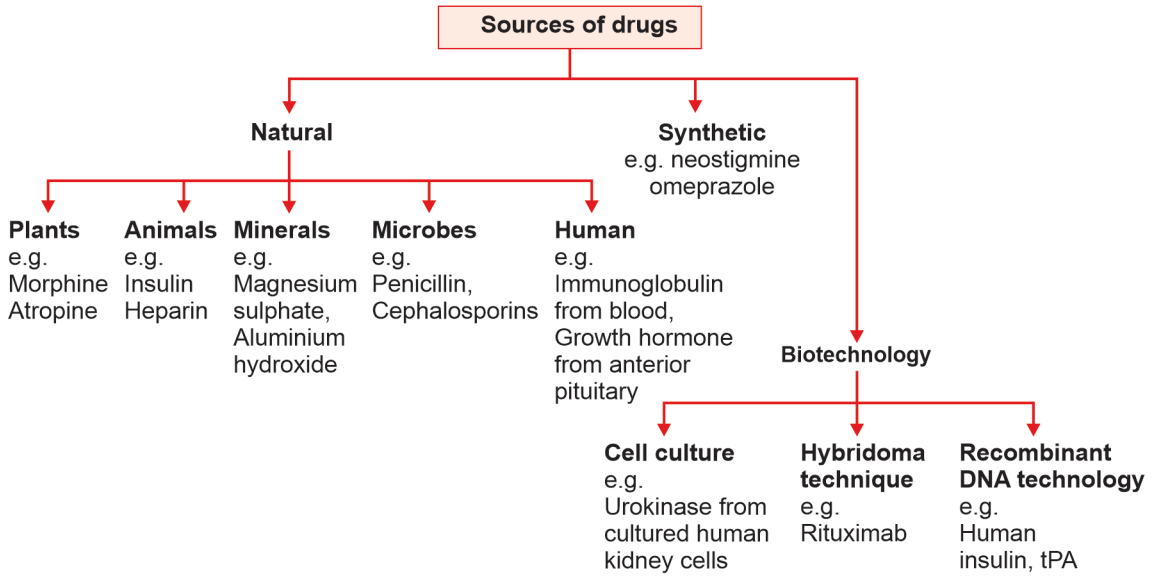
Pharmacopoeia is the official publication containing information on drugs (*see* page 69).

Pharmacy is the science of identification, compounding and dispensing of drugs. It also includes collection, isolation, purification, synthesis and standardization of medicinal substances.

Chronopharmacology is the science that involves the correlation of drug effects to the circadian rhythm to obtain optimum therapeutic effect and minimize the adverse effects, e.g. bronchospasm usually occurs at night. Blood pressure rises at dawn and dusk and is the lowest at midnight (*see* page 70). **Chronotherapy** is the administration of drugs to match the circadian rhythm. **Chronobiotics** are drugs that can be used to modify or reset the circadian rhythm. They find application mostly in conditions like sleep disorders and jet lag.

SOURCES OF DRUGS

The sources of drugs could be natural, or synthetic and biotechnology.



A. NATURAL SOURCES

Drugs can be obtained from:

1. *Plants,* e.g. atropine, morphine, quinine, digoxin, pilocarpine, and physostigmine.
2. *Animals,* e.g. insulin, heparin, gonadotrophins and antitoxic sera.
3. *Minerals,* e.g. magnesium sulphate, aluminium hydroxide, iron, gold, sulphur and radioactive isotopes.
4. *Microorganisms*—antibacterial agents are obtained from some bacteria and fungi, e.g. penicillin, cephalosporins, tetracyclines.
5. *Human*—some drugs are obtained from human source, e.g. immunoglobulins from blood, growth hormone from anterior pituitary and chorionic gonadotrophins from the urine of pregnant women.

B. SYNTHETIC

Most drugs used now are synthetic. They may be manufactured in large quantities and therefore can be less expensive, e.g. quinolones, omeprazole, sulfonamides, pancuronium and neostigmine.

C. BIOTECHNOLOGY

Use of biotechnology in the production of drugs and biologicals has helped to treat many ailments which were once incurable. It has been possible to synthesize many congeners with minor modifications. For example:

- By **cell cultures**, e.g. urokinase from cultured human kidney cells.
- By **recombinant DNA technology**, e.g. human insulin, tissue plasminogen activator, haematopoietic growth factors like erythropoietin, filgrastim and sargramostim.
- By **hybridoma technique**, e.g. monoclonal antibodies like rituximab.

Competency

PH1.2 Describe evidence-based medicine and rational use of drugs and discuss why these are relevant to therapeutics.

EVIDENCE-BASED MEDICINE (EBM)

With the growth of science and the development of scientific methods of research, treatment of diseases now relies largely on scientific evidence obtained from studies.

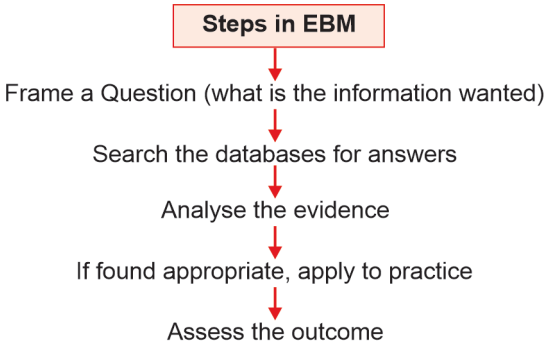
Definition: EBM is applying the best evidence that can be found in the medical literature to medical practice, resulting in the best possible patient care.

Need for EBM: There is high degree of variation in medical practice despite doctors being trained with the same curriculum. With the medical care getting more complex and expensive, it is important to know the best possible care and whenever possible cost-effective treatment.

EBM has 3 components—acquiring information, critical analyse of it and then applying the information to patient care.

Searching the medical literature for best evidence requires good searching skills using medical informatics. It can be time consuming, but many database providers are developing search engines to quickly find reliable and valid information.

The most complex part of the process of EBM is the critical analysis of the medical literature. **Meta-analysis or systematic review** is a relatively new technique that combines many studies on a given topic and analyses them. The TRIP database can be used for a systematic search of nearly 100 evidence-based databases including Medline and Cochrane library and can provide a summary of the results.



Lastly, effectiveness of the practice should also be evaluated before it is incorporated into routine practice.

EBM is a relatively new concept but is now largely popular. Evidence-based practices can be more or less expensive than current practices, but they are better.

Therapeutic drug monitoring is the use of plasma drug levels to guide treatment (*see* page 36).

Competency

PH1.4 Identify the common drug formulations and drug delivery systems, demonstrate their use and describe their advantages and disadvantages.

DRUG FORMULATIONS AND DOSAGE FORMS

Drug formulation is the drug dosage form in which the drug is administered. The right dosage form is important to deliver the drug to the site of action. Drugs may be administered in solid or liquid dosage forms **(Flowchart 1.1)**.

Drug Delivery Systems

Appropriate drug delivery systems are important to attain right drug levels at the site of action. In order to improve drug delivery, to prolong the duration of action and thereby improve patient compliance, **special drug delivery systems** are being tried. Drug targeting, i.e. to deliver drugs at the site where it is required to act is also being aimed at, particularly for anticancer drugs. Some such systems are:

a. *Ocusert:* Ocusert systems are thin elliptical units that contain the drug in a reservoir which slowly releases the drug through a membrane by diffusion at a steady rate, e.g. pilocarpine ocusert used in glaucoma is placed under the lid and can deliver pilocarpine for 7 days.
b. *Progestasert:* Progestasert is inserted into the uterus where it delivers progesterone constantly for over one year.
c. *Transdermal adhesive units:* *See* page 15
d. *Prodrug:* Prodrug is an inactive form of a drug which gets metabolized to the active derivative in the body. Using a prodrug may overcome some of the disadvantages of the conventional forms of drug administration, as follows:

Advantages

1. ***Increase availability at the site***, e.g. dopamine does not cross the BBB; levodopa, a prodrug, crosses the BBB and is then converted to dopamine in the CNS.
2. ***Prolong duration of action:*** Prodrugs may be used to achieve longer duration of action, e.g. bacampicillin (a prodrug of ampicillin) is longer-acting than ampicillin.
3. ***Improve tolerability,*** e.g. cyclophosphamide, an anticancer drug, gets converted to its active metabolite aldophosphamide in the liver. This allows oral administration of cyclophosphamide without causing much gastrointestinal toxicity.
4. ***Drug targeting:*** Zidovudine is taken up by the virus infected cells and gets activated in these cells. This results in selective toxicity to infected cells.
5. ***Improve stability:*** A prodrug may be more stable at gastric pH, e.g. aspirin is converted to salicylic acid which is the more stable active drug and aspirin is also better tolerated than salicylic acid.
6. ***Reduce side effects:*** Prodrug could be used to lower side effects—for example, bacampicillin, a prodrug of ampicillin, is better absorbed and therefore causes less diarrhoea.

Mnemonic for advantages and disadvantages of prodrugs

Mnemonic

TATA Safari for Long Drive

T Tolerability
A Availability
T Targeting possible
A ADR
S Stability better
L in Liver disease—not activated
D Duration of action

Flowchart 1.1: Drug formulations and dosage forms

Solids

1. **Powders** are solid dosage forms in a finely divided state. They may be used for internal administration or for external application, e.g. neomycin powder
2. **Capsules** are solid dosage forms in which the drug is enclosed in a tasteless, hard or soft soluble shell made up of a suitable form of gelatin. They may be spherical, ovoid or cylindrical; Spherical capsules are known as '**pearls**'.
3. **Tablets** are solid dosage forms of medicaments prepared by molding or by compression.
   - Types: Enteric-coated tablets, Sustained-release tablets, Chewable tablets, Dispersible tablets.
4. **Lozenges** are solid dosage forms meant for slow dissolution in the mouth.
5. **Dry syrups** are powders which are to be made into solution before use. Drugs which are not stable in solution are dispensed as dry syrups, e.g. antibiotics including amoxicillin, erythromycin, cephalexin, ampicillin.

Liquids

1. **Solutions** are liquid dosage forms prepared by dissolving a solute in a solvent, e.g. potassium permanganate solution.
2. **Mixture** is a liquid preparation containing two or more substances intended for oral use.
3. **Elixirs** are clear, pleasantly flavored, sweetened liquid preparations for oral use, e.g. chlorpheniramine elixir, paracetamol elixir.
4. **Syrups** are sweet, viscous, aqueous preparations of sugars in an aqueous vehicle.
5. **Suspensions** are liquid dosage forms in which finely divided solid particles (0.5–5.0 microns) are suspended in a liquid or semisolid vehicle using a suspending agent, e.g. barium sulphate suspension, kaolin suspension
6. **Linctuses** are sweet, viscous liquid preparations used for the treatment of cough. Linctuses are swallowed slowly in small doses without addition of water, e.g. codeine linctus, noscapine linctus.
7. **Gargles and mouthwashes**: Gargles are aqueous solutions used for the prevention or treatment of throat infections. Mouthwashes are aqueous solutions for deodorizing and refreshing the oral cavity.
8. **Tinctures** are alcoholic liquid preparations prepared by dissolving the corresponding liquid extract in solvents, e.g. belladonna tincture, opium tincture.
9. **Emulsions** are liquid dosage forms in which two immiscible liquids are made miscible with the help of an emulsifying agent. Labeled with 'shake the bottle before use, e.g. phenolphthalein emulsion.
10. **Liniments** are liquid or semiliquid preparations meant for external application to the skin with friction but should not be applied to the broken skin.
11. **Lotions** are liquid suspensions meant for external application without friction.

Others

1. **Aerosols:** Pressurized dosage forms in which the liquid or solid drugs are dissolved or suspended in gas. They bring about fine dispersion of liquid (mist) or solid particles of size less than 50 microns in diameter, e.g. drugs for bronchial asthma, deodorant sprays, cosmetic hair sprays.
2. **Semisolids:** Ointments are soft semisolid preparations meant for external application to the skin or mucous membrane. Creams are viscous semisolid emulsions meant for application to skin. Creams are lighter than ointments.
3. **Enemas** are aqueous or oily solutions or suspensions intended for introduction into the rectum.
4. **Injections** are liquid preparations containing one or more medicaments dissolved or suspended in a suitable vehicle and are meant for introduction into the body tissues with the help of a syringe and needle, e.g. ampicillin injection, dextrose intravenous infusion.
5. **Suppositories** are special shaped solid dosage forms for insertion into body cavities other than mouth. They may be inserted into rectum, vagina or urethra, e.g. clotrimazole suppository.

Disadvantages

1. Prodrugs are likely to have a slower onset of action and therefore are not suitable in emergencies.
2. In presence of liver diseases prodrugs may not be activated to attain therapeutic levels.

e. ***Osmotic pumps:*** These are small tablet-shaped units containing the drug and an osmotic substance in two different chambers. The tablet is coated with a semipermeable membrane in which a minute laser-drilled hole is made. When the tablet is swallowed and reaches the gut, water enters into the tablet through the semipermeable membrane. The osmotic layer swells and pushes the drug slowly out of the laser-drilled orifice. This allows slow and constant delivery of the drug over a long period of time. It is also called gastrointestinal therapeutic system (GITS). Some drugs available in this formulation are iron and prazosin.

f. ***Computerised miniature pumps:*** These are programmed to release drugs at a definite rate either continuously as in case of insulin or intermittently in pulses as in case of GnRH.

Various methods of drug targeting are tried especially for anticancer drugs to reduce toxicity.

g. ***Targeted drug delivery systems:*** In the last decade, efforts have been made to deliver drugs to the site of action. Such drug targeting is the dream of any pharmacologist, since it would mean a remarkable progress in therapeutics. Drug targeting largely reduces the adverse drug reactions because the required amount of the drug will be delivered at the required site of action.

Some of the targeted delivery systems currently available are:

i. ***Liposomes*** are phospholipids suspended in aqueous vehicles to form minute vesicles. They are used as carriers for both water-soluble and lipid-soluble substances as they can be entrapped in the aqueous spaces or within the lipid layer itself. For example, a lipid is hydrated with an aqueous solution of the drug.

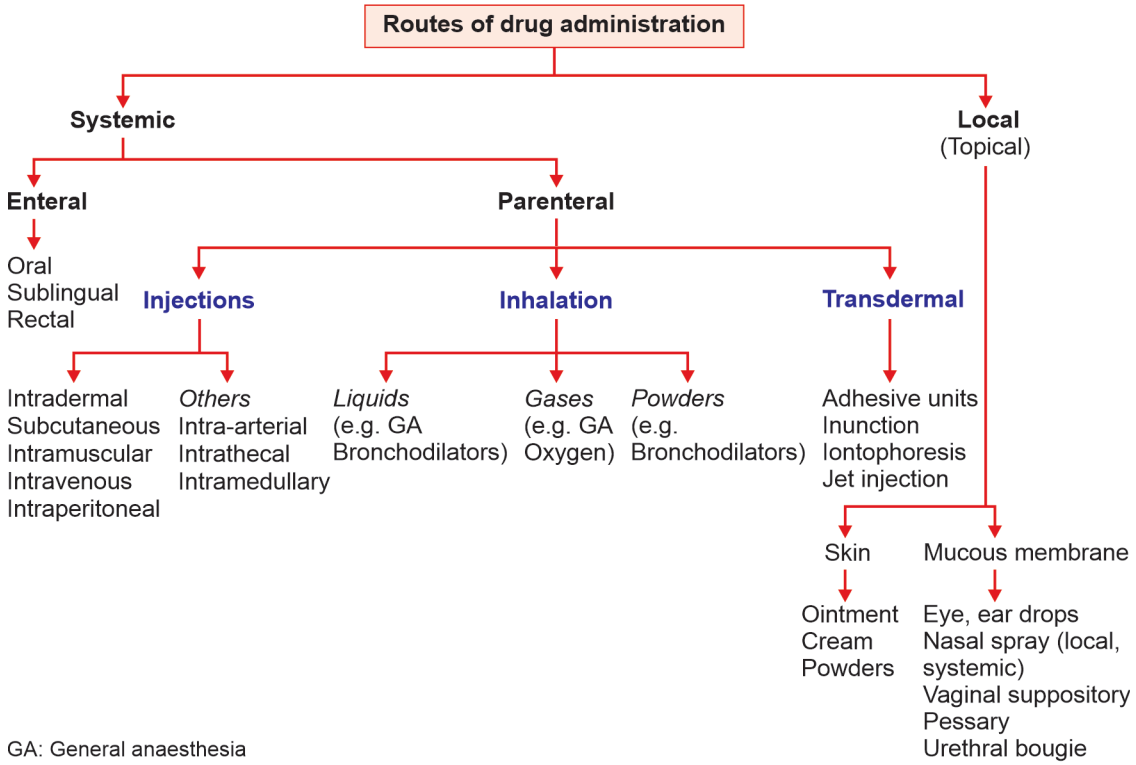
Though liposomes can be given both orally and parenterally, IV route is the most common. Small liposomes are taken up by the reticuloendothelial cells while larger ones are deposited in the lungs and are also concentrated in malignant tumours. Thus site-specific delivery of drugs may be possible with the help of liposomes. Liposomes are used in the treatment of cancers, systemic fungal infections, diabetes mellitus and in heavy metal poisoning. Examples of some liposomes available are doxorubicin, cytarabin, cisplatin and irinotecan.

ii. ***Monoclonal antibodies*** against the tumour-specific antigens are used to deliver anticancer drugs to specific tumour cells.

iii. ***Nanoparticles:*** The drug is encapsulated or dissolved in the nanoparticle (NP) matrix to obtain nanocapsules or nanoparticles. The size of the nanoparticles vary from 10 to 1000 nm and are biogradable. They can be used to deliver the anticancer drugs to the cancer tissue in order to improve efficacy and reduce toxicity.

iv. ***Polymer-based drug delivery:*** Polymers have been used in transdermal drug delivery systems. Polymers are used for coating as in enteric-coated capsules and drug eluting stents. Drugs are also designed to be delivered directly to the colon in ulcerative colitis and inflammatory bowel disease.

v. ***Drug eluting stents*** are devices consisting of a metallic stent (tubular mesh-like device) coated with a drug on a polymer coating. The drug may be sirolimus or paclitaxel. The drug is gradually released over 4–6 weeks and prevents the proliferation of vascular smooth muscles and endothelial cells over the stent placed.



GA: General anaesthesia

ROUTES OF DRUG ADMINISTRATION

Competency

PH1.5 Describe various routes of drug administration, their advantages and disadvantages and demonstrate administration of, e.g. SC, IV, IM, SL, rectal, spinal, sublingual, intranasal sprays and inhalers.

Drugs may be administered by various routes. The choice of the route in a given patient depends on the properties of the drug and the patient's requirements. A knowledge of the advantages and disadvantages of the different routes of drug administration is essential for appropriate use of drugs.

The routes can be broadly divided into:

- Systemic routes
- Local/topical routes.

SYSTEMIC ROUTES

Enteral Route

Enteral routes include oral, sublingual and rectal routes.

1. Oral Route

Oral route is the most commonly used, oldest and safest route of drug administration. The large surface area of the gastrointestinal tract, the mixing of its contents and the differences in pH at different parts of the gut facilitate effective absorption of the drugs given orally.

However, the acid and enzymes secreted in the gut and the biochemical activity of the bacterial flora of the gut can destroy some drugs before they are absorbed.

Advantages

1. Safest route
2. Most convenient
3. Most economical
4. Drugs can be self-administered
5. Non-invasive route.

Disadvantages

1. **Slow action:** Onset of action is slower as absorption needs time—hence particularly not suitable for emergencies.

2. **Drug properties:** Irritant and unpalatable drugs cannot be administered.
3. **Poor absorption:** Some drugs may not be absorbed due to certain physical and chemical characteristics, e.g. streptomycin is not absorbed orally.
4. **GI irritation:** Irritation to the gastrointestinal tract may lead to vomiting.
5. **Unpredictable absorption:** There may be irregularities in absorption.
6. **Metabolism:** Some drugs may be destroyed by gastric juices, e.g. insulin.
7. **Unsuitable situations:** Oral preparations cannot be given to unconscious and uncooperative patients.
8. **First-pass effect:** Some drugs may undergo extensive first pass metabolism in the liver.

To overcome some of the disadvantages, irritants are given in capsules, while bitter drugs are given as sugar-coated tablets. Sometimes drugs are coated with substances like synthetic resins, gums, sugar, colouring and flavouring agents, making them more acceptable.

Enteric-coated tablets: Some tablets are coated with substances or polymers like cellulose-acetate, phthalates, gluten, shellac, etc. which are not digested by the gastric acid but get disintegrated in the alkaline juices of the intestine. The choice of the polymer and the thickness of coating influence the dissolution of the coat in the intestines. Enteric coating will:

1. Prevent gastric irritation
2. Avoid destruction of the drug in the stomach
3. Provide higher concentration of the drug in the small intestine
4. Retard the absorption, and thereby prolong the duration of action.

However, if the coating is inappropriate, the tablet may be expelled without being absorbed.

Similarly, **controlled-release** or **sustained-release preparations** are designed to prolong the rate of absorption and thereby the duration of action of the drugs **(Fig. 1.1)**. This is useful for short-acting drugs. In newer controlled release formulations, the tablet is coated with a semipermeable membrane through which water enters and displaces the drug out.

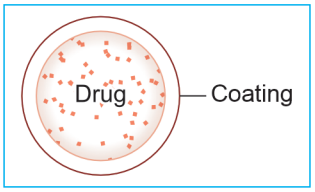


Fig. 1.1: Sustained release preparation. Dissolution of coating depends on the thickness and stability of the coat

Advantages

- Frequency of administration may be reduced.
- Therapeutic concentrations may be maintained specially when nocturnal symptoms are to be treated.

Disadvantages

- There may be 'failure of the preparation' resulting in release of the entire amount of the drug in a short time, leading to toxicity.
- Enteric coated tablets are more expensive.

Certain precautions are to be taken during oral administration of drugs—capsules and tablets should be swallowed with a glass of water with the patient in upright posture either sitting or standing. This facilitates passage of the tablet into the stomach and its rapid dissolution. It also minimises the chances of the drug getting into the larynx or behind the epiglottis. Recumbent patient should not be given drugs orally as some drugs may remain in the oesophagus due to the absence of gravitational force facilitating the passage of the drug into the stomach. Such drugs can damage the oesophageal mucosa, e.g. iron salts, tetracyclines.

2. Sublingual

Here, the tablet or pellet containing the drug is placed under the tongue. As the drug dissolves, it is absorbed across the sublingual mucosa, e.g. nitroglycerin, nifedipine, buprenorphine. The tablet may also be crushed in the mouth but not swallowed and the contents are absorbed

across the buccal mucosa. The formulation should be so designed that it quickly dissolves in the saliva. The buccal mucosa is rich in blood supply. This allows quick absorption of the drug.

Advantages

1. Absorption is rapid—within minutes the drug reaches the circulation.
2. First-pass metabolism is avoided because the drug directly reaches the systemic circulation.
3. After the desired effect is obtained, the drug can be spat out to avoid the unwanted effects.

Disadvantages

1. Buccal ulceration can occur.
2. Lipid-insoluble drugs, drugs of higher molecular weight, irritant and unpalatable drugs cannot be given by this route.

3. Rectal

Rectum has a rich blood supply and drugs can cross the rectal mucosa to be absorbed for systemic effects. Drugs absorbed from the upper part of the rectum are carried by the superior haemorrhoidal vein to the portal circulation (can undergo first pass metabolism), while that absorbed from the lower part of the rectum is carried by the middle and inferior haemorrhoidal veins to the systemic circulation. Drugs like indomethacin, chlorpromazine, diazepam and paraldehyde can be given rectally.

Some irritant drugs are given rectally as suppositories.

Advantages

1. Gastric irritation is avoided.
2. Can be administered by unskilled persons.
3. Useful in geriatric patients; patients with vomiting, those unable to swallow and after gastrointestinal surgery.
4. Also useful in unconscious patients.

Disadvantages

1. Irritation of the rectum can occur.
2. Absorption may be irregular and unpredictable.

Drugs may also be given by rectal route as enema.

Enema is the administration of a drug in a liquid form into the rectum. Enema may be evacuant or retention enema.

Evacuant enema: In order to empty the bowel, about 600 ml of soap water is administered per rectum. Water distends and thus stimulates the rectum while soap lubricates. Enema is given prior to surgeries, obstetric procedures and radiological examination of the gut.

Retention enema: The drug is administered with about 100 ml of fluids and is retained in the rectum for local action, e.g. prednisolone enema in ulcerative colitis.

Parenteral Routes

Routes of administration other than the enteral (intestinal) route are known as parenteral routes. Here the drugs are directly delivered into the tissue fluids or blood.

Advantages

1. Action is more rapid and predictable than oral administration.
2. These routes can be employed in an unconscious or uncooperative patient.
3. Gastric irritants can be given parenterally and, therefore, irritation to the gastrointestinal tract can be avoided.
4. It can be used in patients with vomiting or those unable to swallow.
5. Digestion by the gastric and intestinal juices and the first pass metabolism are avoided.

Therefore, in emergencies, parenteral routes are very useful for drug administration as the action is rapid and predictable and are useful even in unconscious patients.

Disadvantages

1. Asepsis must be maintained
2. Injections may be painful
3. More expensive, less safe and inconvenient
4. Injury to nerves and other tissues may occur.

Parenteral routes include:

1. Injections
2. Inhalation
3. Transdermal route

1. Injections

Injections are given with the help of syringe and needle.

Intradermal: The drug is injected:

- Into the layers of the skin raising a bleb, e.g. BCG vaccine, tests for allergy.
- By multiple punctures of the epidermis through a drop of the drug, e.g. smallpox vaccine. Only a small quantity can be administered by this route and it may be painful.

Subcutaneous (SC) injection: Here, the drug is deposited in the SC tissue, e.g. insulin, heparin. As this tissue is less vascular, absorption is slow and largely uniform, making the drug long-acting. It is reliable and patients can be trained for self-administration. Absorption can be enhanced by the addition of the enzyme hyaluronidase.

Disadvantages

1. As SC tissue is richly supplied by nerves, irritant drugs cannot be injected because they can cause severe pain.
2. In shock, absorption is not dependable because of vasoconstriction.
3. Repeated injections at the same site can cause lipoatrophy resulting in erratic absorption.

Hypodermoclysis is the subcutaneous administration of large volumes of saline employed in paediatric practice.

Drugs can also be administered subcutaneously as:

i. ***Dermojet:*** In this method, a high velocity jet of drug solution is projected from a fine orifice using a 'gun'. The solution gets deposited in the SC tissue from where it is absorbed. As needle is not required, this method is painless. It is suitable for vaccines.

ii. ***Pellet implantation:*** Small pellets packed with drugs are implanted subcutaneously. The drug is slowly released for weeks or months to provide constant blood levels, e.g. testosterone, desoxycorticosterone acetate (DOCA).

iii. ***Sialistic implants:*** The drug is packed in sialistic tubes and implanted subcutaneously. The drug gets absorbed over months to provide constant blood levels, e.g. hormones and contraceptives. The empty non-biodegradable implant has to be removed.

Intramuscular (IM): Aqueous solution of the drug is injected into one of the large skeletal muscles—deltoid, triceps, gluteus or rectus femoris. Absorption into the plasma occurs by simple diffusion. Larger molecules enter through the lymphatic channels. As the muscles are vascular, absorption is rapid and quite uniform. Drugs are absorbed faster from the deltoid region than gluteal region especially in women. The volume of injection should not exceed 10 ml. For infants, rectus femoris is used instead of gluteus because gluteus is not well-developed till the child starts walking. If the drug is injected as oily solution or suspension, absorption is slow and steady and can have prolonged effect. Soluble substances, mild irritants, depot preparations, suspensions and colloids can be injected by this route.

Advantages

1. Intramuscular route is reliable.
2. Absorption is rapid.

Disadvantages

1. Intramuscular injection may be painful
2. May even result in an abscess. Local infection and tissue necrosis are possible.
3. Nerve injury should be avoided—irritant solutions can damage the nerve, if injected near a nerve.
4. In case of some drugs, absorption by IM route is slower than oral, e.g. diazepam, phenytoin.

5. For some drugs, IM route should be avoided, e.g. heparin, calcium gluconate, diazepam, and tetracycline.

Intravenous (IV): Here, the drug is injected into one of the superficial veins so that it directly reaches the circulation and is immediately available for action. Drugs can be given IV as:

1. ***A bolus:*** Where an initial large dose (loading dose) is given, e.g. heparin. The drug is dissolved in a suitable amount of the vehicle and injected slowly.
2. Slow injection—over 15–20 minutes, e.g. aminophylline.
3. Slow infusion—when constant plasma concentrations are required, e.g. oxytocin in labour or when large volumes have to be given, e.g. dextrose, saline. Generally, about one litre of solution is infused over 3–4 hours. However, the patient's condition and the drug factors like the onset and duration of action of the drug dictate the rate of infusion.

Advantages

1. Most useful route in emergencies as the drug is immediately available for action.
2. Provides predictable blood concentrations with 100% bioavailability.
3. Large volumes of solutions can be given.
4. Irritants can be given by this route as they get quickly diluted in blood.
5. Rapid dose adjustments are possible—if unwanted effects occur, infusion can be stopped; if higher levels are required, infusion rate can be increased—specially for short-acting drugs.

Disadvantages

1. Once injected, the drug cannot be withdrawn.
2. Irritation of the veins may cause thrombophlebitis.
3. Extravasation of some drugs may cause severe irritation and sloughing.
4. Only aqueous solutions can be given IV but not suspensions, oily solutions and depot preparations.
5. Self-medication is difficult.
6. Risk of embolism—though rare.

Intraperitoneal: Peritoneum offers a large surface area for absorption. Fluids are injected intraperitoneally in infants. This route is also used for peritoneal dialysis.

Other injections: Intrathecal: Drugs can be injected into the subarachnoid space for action on the CNS, e.g. spinal anaesthetics. Some antibiotics and corticosteroids are also injected by this route to produce high local concentrations. Strict aseptic precautions are a must.

Drugs are also given extradurally. Morphine can be given epidurally to produce analgesia. Direct intraventricular administration of drugs may be employed in brain tumors.

Intra-articular: Drugs are injected directly into a joint for the treatment of arthritis and other diseases of the joints, e.g. in rheumatoid arthritis, hydrocortisone is injected into the affected joint. Strict aseptic precautions are required.

Intra-arterial: Intravenous and intra-arterial are intravascular routes. In intra-arterial route, the drug is injected directly into the arteries. It is used only in the treatment of:

1. Peripheral vascular diseases
2. Local malignancies
3. Diagnostic studies like angiograms.

Intramedullary: Injection into a bone marrow—now rarely used.

2. Inhalation

Lungs offer a large surface area for absorption of drugs. Volatile liquids and gases are given by inhalation, e.g. general anaesthetics. In addition, drugs can be administered as solid particles, i.e. solutions of drugs can be atomised and the fine droplets are inhaled as aerosol, e.g. salbutamol. These inhaled drugs and vapours may act locally on the pulmonary epithelium and mucous membranes of the respiratory tract or may also be absorbed

through these membranes. The drug delivery by this route is influenced by the particle size and the breathing pattern. Drugs for inhalation are available as metered dose inhalers (MDI), dry powder inhalers (DPI) and nebulizers. In a metered dose inhaler, a solution containing multiple doses of particles of the drug, along with a propellant is stored under high pressure in a container. When the inhaler is activated, a fixed amount of the drug jets out of an orifice as a mist. In a dry powder inhaler, the drug is stored in a dry powder form. Nebulizers have the advantages that they do not require a propellant and the drug is delivered as small droplets which are breathed into the lungs.

Advantages

1. Almost instantaneous absorption of the drug is achieved because of:
   - The large surface area of the lungs
   - Thin alveolar membrane
   - High vascularity
2. In pulmonary diseases, inhalation serves almost as a local route as the drug is delivered at the desired site making it more effective and less harmful.
3. Because the drug is directly delivered, smaller dose is needed and, therefore, toxicity is much less.
4. Hepatic first pass metabolism is avoided.
5. Blood levels of volatile anaesthetics can be conveniently controlled as their absorption and excretion through the lungs are governed by the laws of gases.

Disadvantages

1. Irritant gases may enhance pulmonary secretion—should be avoided.
2. Drug particles may induce cough, e.g. cromolyn sodium.

This is an important route of entry of certain drugs of abuse.

3. Transdermal

Highly lipid-soluble drugs can be applied over the skin for slow and prolonged absorption, e.g. nitroglycerine ointment in angina pectoris. Adhesive units, inunction, iontophoresis and jet injection are some forms of transdermal drug delivery.

Adhesive units: Transdermal adhesive units (transdermal therapeutic systems) are adhesive patches **(Fig. 1.2)** of different sizes and shapes made to suit the area of application. The drug is held in a reservoir between an outer polymer layer and a porous membrane. The under surface of the membrane is smeared with an adhesive to hold on to the area of application. The drug slowly diffuses through the membrane and percutaneous absorption takes place. The rate of absorption is constant and predictable. Highly potent drugs (because small quantity is sufficient) and short-acting drugs (because effect terminates quickly after the system is removed) are suitable for use in such systems.

Sites of application depend on the indication—they may be applied over the chest, abdomen, upper arm, back or mastoid region; testosterone patch is applied over the scrotum.

For examples: Hyoscine, nitroglycerin, testosterone, oestrogen, nicotine and fentanyl transdermal patches **(Table 1.1)**.

Advantages

1. Duration of action is prolonged
2. Provides constant plasma drug levels
3. Patient compliance is good.

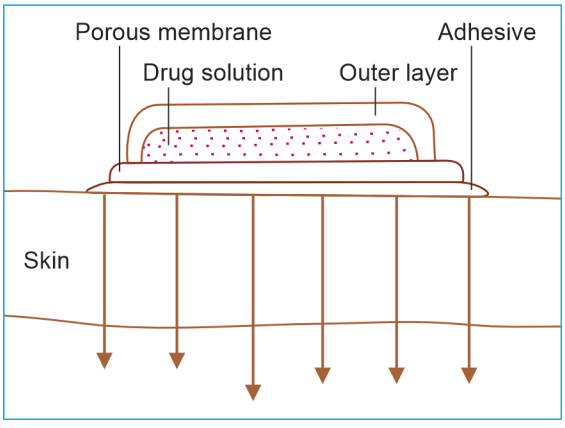


Fig. 1.2: Transdermal adhesive unit

Table 1.1: Transdermal therapeutic system—some examples

Drug	Site	Indication
Nitroglycerin	Chest	Angina pectoris
Scopolamine	Mastoid region	Travelling sickness
Estrogen	Waist	Post-menopausal syndrome
Nicotine	Forearm/arm	To stop smoking
Testosterone	Scrotum, back, thigh	Deficiency
Fentanyl	Upper arm/back	Analgesic

Disadvantages

1. Large doses of the drug cannot be loaded into the system
2. Can cause irritation to the skin
3. Expensive.

Inunction: The route where a drug rubbed into the skin gets absorbed to produce systemic effects is called inunction.

Iontophoresis: Since flow of electricity enhances the permeability of the skin, in this procedure, galvanic current is used for bringing about penetration of lipid-insoluble drugs into the deeper tissues where their action is required, e.g. salicylates. Fluoride iontophoresis is used in the treatment of dental hypersensitivity.

Jet injection: As absorption of the drug occurs across the layers of the skin, dermojet may also be considered as a form of transdermal drug administration.

LOCAL/TOPICAL APPLICATION

Drugs may be applied on the skin for local action as ointment, cream, gel, powder, paste, etc. Drugs may also be applied on the mucous membrane as in the eyes, conjunctiva, ears and nose as ointment, drops and sprays.

Nasal: Drugs can be administered through nasal route either for systemic absorption or for local effects.

For example, for systemic absorption, oxytocin spray is used.

For local effect—decongestant nasal drops, e.g. oxymetazoline, budesonide nasal spray for allergic rhinitis.

Many drugs are administered as **suppository** for rectum, **bougie** for urethra and **pessary** and douche for vagina. Pessaries are oval-shaped tablets to be placed in the vagina to provide high local concentrations of the drug at the site, e.g. antifungal pessaries in vaginal candidiasis.

Douche is an aqueous solution used for rinsing a body cavity. Though the word 'douche' is generally used for vaginal solutions, it can also be used for solutions meant for bladder or the rectum.