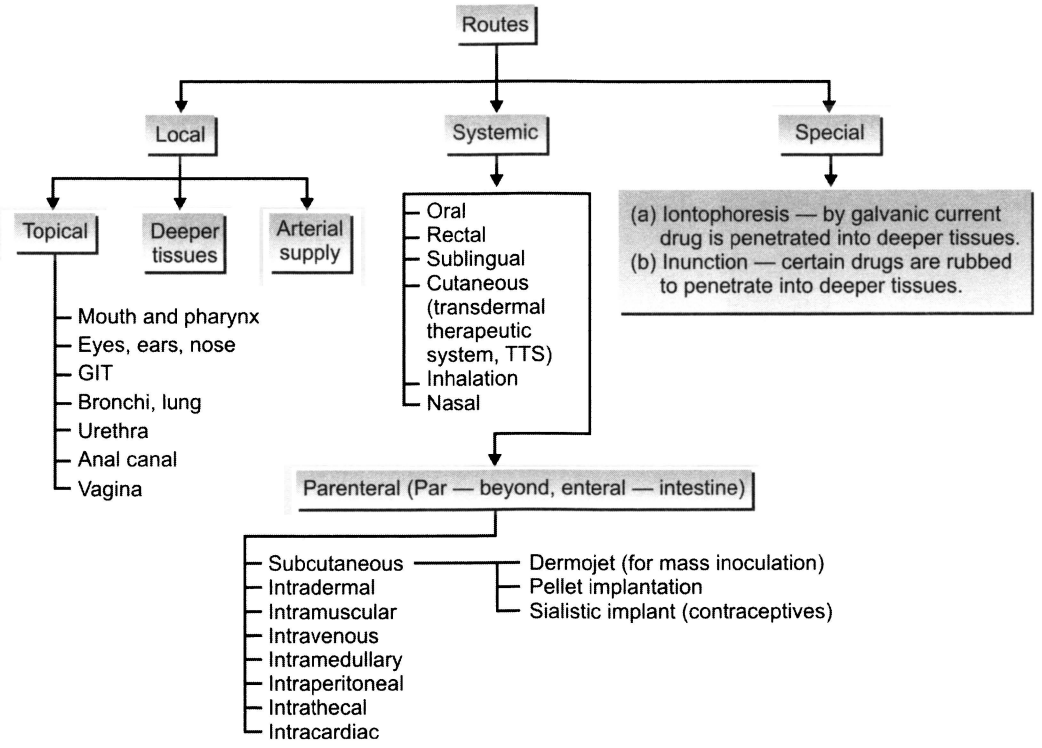
Flowchart 1.1: Routes of drug administration (Figs 1.2 to 1.7)



Flowchart 1.2: Some characteristics of common routes of drug administration

Routes

	Intravenous	Subcutaneous	Intramuscular	Oral
Absorption	• 100% • Immediate effect	• Prompt • Slow for sustained form • Repository preparation	• Prompt for aqueous solution	• Variable
Special Utility	• Emergency • Permits titration of doses • Suitable for large volume and irritating substance	• Suitable for insoluble and for solid pellets	• Suitable for moderate volume, oily vehicles, irritating substances	• Most convenient • Economical • Safe
Limitations	• Increased risk of adverse effects • Not suitable for insoluble substances	• Not suitable for large volume	• May interfere with interpretation of some diagnostic tests, *viz.* CPK may be increased.	• Requires patients cooperation • Availability variable; depends on hepatic metabolism.

Routes of excretion may be:

1. Urine (depends on glomerular filtration, tubular secretion and reabsorption)
   - Glomerular filtration depends upon plasma protein binding and renal blood flow. Tubular secretion depends upon plasma protein binding. In the nephron separate pumps operate to secrete acidic and basic drugs. Lipid solubility of the drug determines tubular resorption and lipid solubility depends on ionization. Ionized drug excretes *via* kidney.
2. Feces
3. Lungs
4. Saliva and sweat
5. Milk (may produce toxicity to infant fed on milk)

KINETICS OF ELIMINATION

Clearance: It is the theoretical volume of plasma from which drug is completely removed in unit time. Clearance like volume of distribution may be in respect to blood (Clb); plasma (Clp) and unbound in water (Clu). Systemic clearance = (Cl renal) + (Cl liver) + (Cl other).

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

Say plasma concentration is 8 mg/mL and rate of elimination 400 mg/min then rate of eliminaton is 50 mL/min.

- **First order kinetics:** A constant fraction of drug is eliminated in unit time. Hence full drug is dissolved in GI fluid and rate of absorption is proportional to GI fluid. It can be estimated by area under curve (AUC). At low doses drug metabolism is first order. t½ and clearance are constant in first order kinetics and rate of elimination is proportional to plasma concentration. Here plasma fallout curve is curvilinear and log plasma fallout curve is linear (Figs 2.7–2.9).
- **Zero order kinetics:** A constant amount is eliminated per unit time. Here rate of absorption is independent of amount of drug in the gut, but determined by rate of gastric emptying or controlled release formulation. Ethyl alcohol is eliminated by zero order kinetics. Elimination of some drugs approaches saturation over therapeutic range and their kinetics change from first order to zero order.

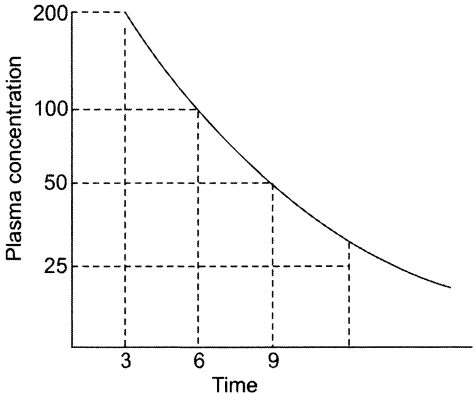


Fig. 2.7

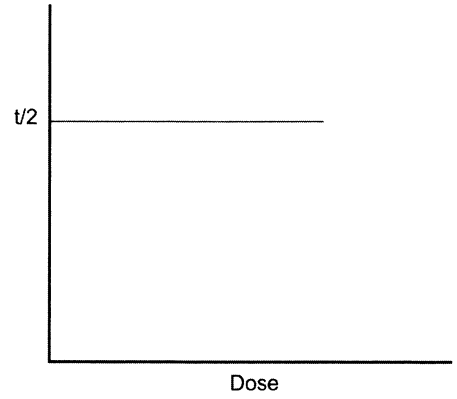


Fig. 2.8

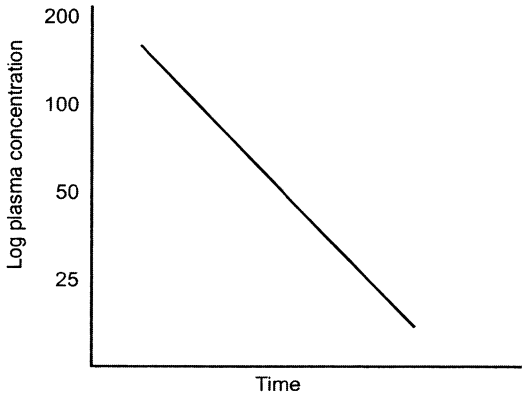
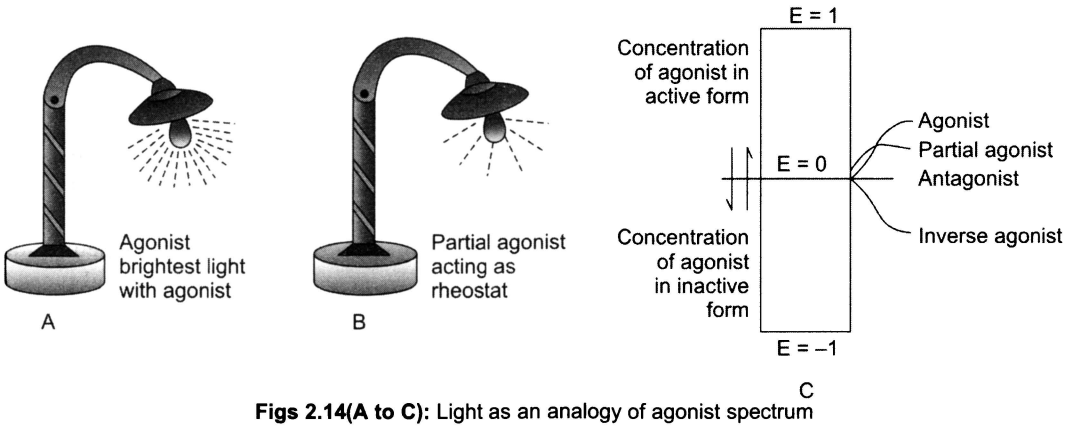


Fig. 2.9: Log plasma fallout curve in first order kinetics



Figs 2.14(A to C): Light as an analogy of agonist spectrum

Partial agonist: It has intermediate intrinsic activity producing submaximal effect at full receptor occupancy. (Fig. 2.15)

Antagonist: It combines with receptor, but without intrinsic activity or zero, *i.e.* binds to receptor and prevents its binding to other molecule, *viz.* atropine antagonizes the action of acetylcholine binding with muscarinic receptor. (Fig. 2.15)

Inverse agonist: These drugs have affinity for the receptor, but intrinsic activity, a minus sign, *e.g.* DMCM on benzodiazepine receptor, *i.e.* inverse agonist do the opposite of agonists.

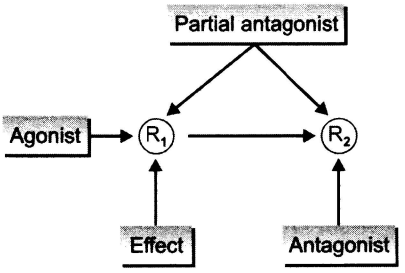


Fig. 2.15

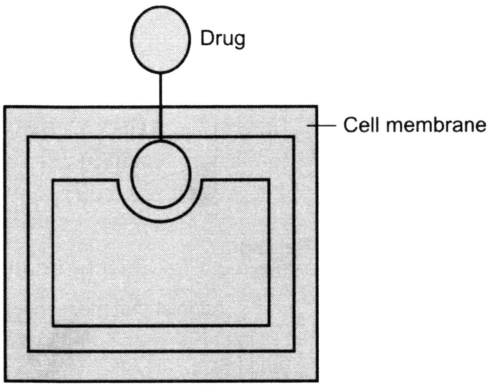


Fig. 2.16

Functions of Receptor

1. To propagate regulatory signals from outside to inside of effecter cells and to amplify it.
2. To integrate various extracellular to intracellular regulatory signals.
3. To adopt short-term and long-term changes in the regulatory milieu to maintain hemostasis.

Receptor Theories of Drug Action

i. Occupation theories of Clark

$$\text{Drug} + [A] + \text{Receptor } [R] \underset{K_2}{\overset{K_1}{\rightleftharpoons}} AR \xrightarrow{K_3} \text{Response}$$

In affinity, the association : dissociation constant is one and determines potency, K_3 determines maximal effect of agonist.

ii. Rate theory of Paton: Response is the function of rate of association between drug molecule and receptors. Drug with high dissociation constant K_2 is agonist, low K_2 is antagonist and which has intermediate K_2 is partial antagonist.

iii. Two state receptor model: Receptor exists in two interchangeable states R_1 and R_2. Agonist binds to R_1 to produce effect. Antagonist binds to R_2. Partial antagonist binds to both R_1 and R_2 (Fig. 2.15).

a. **Synergism:** Here one drug effect is facilitated by others. It may be:
   - **Additive:** The sum of two drugs response is equal to the algebraic sum of them, *viz.* Aspirin + Paracetamol.
   - **Potentiation:** When response is more than sum of their individual response.

b. **Antagonism:** Here one drug inhibits the action of another. The antagonism may be:
   - **Physical:** Charcoal adsorbs alkaloids due to its physical properties.
   - **Chemical:** Acid + Alkali.
   - **Competitive:** Atropine in muscarinic poisoning.
   - **Non-competitive:** DFP + Acetylcholine.
   - **Therapeutical:** Physiological histamine induced bronchospasm antagonized by adrenaline.

Drug Interactions

When two drugs are given simultaneously or one after another they may interact. The drug interaction is generally harmful to the patient so proper precaution has to be taken to reduce it.

Some examples of therapeutically desirable drug interactions

- **Addition:** Dopaminergic + Anticholinergic in the treatment of parkinsonism.
- **Synergistic:** Cotrimoxazole as antimicrobials.
- **Augmentative:** Penicillin + Probenecid or Carbidopa + Levodopa.
- **Facilitative:** Penicillin + Aminoglycosides
- **Reparative:** Aluminum + Mg salt for acid neutralization for smooth regular bowel as antacids.

Drug Screening

Regardless the source of drug molecule, the sequence of repeatative experimentation and characterization is called drug screening to define its pharmacological profile at molecular to origin level. Result of desired screening produces "lead compound", a successful new drug.

Expiry Date of a Drug

It is a legal requirement that all pharmaceutical products carry date of manufacturing and date of expiry, the period in between is called **life period.** The Drug and Cosmetic Act specifies the life period between 1–5 years. Self-life is dependent on drug itself and its storage condition. Drugs are not allowed beyond expiry date legally though they are not always toxic.

Pharmacovigilance

WHO has defined pharmacovigilance "as science and activities related to detection, assessment, understanding and preventing ADR or any drug related problem". Its activities include post-marketing surveillance, spreading of ADR data through drug alerts, labeling of medicine with warning and drug withdrawal. Pharmacovigilance center is present in almost all the countries. The Uppsala Monitoring Center in Sweden is an international collaborating center. In India, national collaborating center is present in the All India Institute of Medical Sciences (AIIMS). These centers are expected to provide standard algorithm and rating scales.

Counterfeit Medicine

A medicine is counterfeit, if produced with intention to cheat, *viz.* mislabeling, fudging expiry date, wrong ingredient or no ingredient or correct ingredient in insufficient quantity.

Central drug standard control organization is responsible for safety, efficacy, quality of drugs, their import, manufacture, distribution sale and standard of drugs.

Over the Counter (OTC) Drugs

In some advanced countries the drugs are divided by laws into those restricted to sale by prescription only and those which may be sold without prescription also are called OTC drugs. The knowledge of OTC drugs by general practitioner or by specialist is important because:

i. Some of the OTC products are cheaper.
ii. Some OTC drugs may worsen the clinical situation.