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Tiruchirappalli- 620024, Tamil Nadu,
India

Programme: M.Sc., Biomedical Science

Course Title : Drug Discovery and Assay Development
Course Code : 18BMS48ES

Unit-II

Drug Action and Classification

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A drug is defined as:

- Recognized by an official pharmacopeia or formulary.
- Use - Diagnosis, cure, mitigation, treatment, prevention.
- To affect the structure or function of the body.
- Biological products

  (chemical process vs biological process).

- Trade or proprietary name (Lipitor)
- Generic or nonproprietary name (Atorvastatin)
- Chemical name for the active ingredient

  [*R-(R*,R*)]*-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate).
- The International Nonproprietary Names (INN) of the World Health Organization (WHO)

By Chemical Structure

- Drugs are classified according to the chemical moiety or functional group.
- *Hydrocarbons*
- *Halogenated compounds*
- *Alcohols*
- *Carboxylic acids*
- *Phenols*
- *Nitro compounds*
- *Amides*
- *Amines*
- *Sulphonamides, sulphones, stilbenes, thioureas, ureides etc*

Affect the normal dynamic processes of the body.

(*i) Anti-arrhythmics*
(*ii) Antianginals*
(*iii) Vasodialators*
(*iv) Anti-hypertensives*
(*v) Cardiotonics*
(*vi) Hypocholesteric agents*
(*vii) Antiallergic agents*
(*viii) Drugs acting on GIT*
(*ix) Drugs influence renal function*
(*x) Drugs acting on central nervous system*
(*xi) Drugs acting on peripheral nervous system*

I. Enzyme inhibition

- **Drugs act within the cell by modifying normal biochemical reactions.**
- Enzyme inhibition may be reversible or non-reversible; competitive or non-competitive.
- Antimetabolites may be used which mimic natural metabolites.

2. Drug-Receptor interaction

- **Drugs act on the cell membrane by physical and/or** chemical interactions.
- This is usually through specific drug receptor sites known to be located on the membrane.
- A receptor is the specific chemical constituents of the cell with which a drug interacts to produce its pharmacological effects.
- Some receptor sites have been identified with specific parts of proteins and nucleic acids.

3. Non-specific interactions

- **Drugs act exclusively by physical means outside of cells.**
- These sites include external surfaces of skin and gastrointestinal tract.
- Drugs also act outside of cell membranes by chemical interactions.
- Neutralization of stomach acid by antacids is a good example.

MODE OF ACTION

- It is important to distinguish between actions of drugs and their effects.
- Actions of drugs are the Biochemicals, physiological mechanisms by which the chemical produces a response in living organisms.
- Action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of bacteria.

- The primary effect is the desired therapeutic effect.
- Secondary effects are all other effects beside the desired effect which may be either beneficial or harmful.

l. Killing foreign organisms.

Chemotherapeutic agents act by killing or weakening foreign organisms such as bacteria, worms, and viruses. The main principle of action is selective toxicity, i.e. the drug must be more toxic to the parasite than to the host.

2. Stimulation and depression. Drugs act by stimulating or depressing normal physiological functions. Stimulation increases the rate of activity while depression reduces it.

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3. **Irritation. It is a non-specific action of a drug that can occur in all the body tissues.**

   Certain drugs act by causing irritation. Ex: Drugs like senna and castor oil show their laxative effects by their irritant action on gastrointestinal tract.

4. **Replacement. Drugs serve as replacement of essential body chemicals that are either**

   absent or present in less than required quantity due to disease. Ex: Insulin is used in diabetes. Levodopa therapy in Parkinson's disease

A drug act by virtue of its various properties like physical, chemical, physiological etc.

1. **Physical Properties**

   (*i) **Taste.** Bitter taste drugs increase the flow the hydrochloric acid reflexly in the stomach.*

   Ex: Quassia, Chirata

   (*ii) **Mass**. By increasing the bulk of drug in intestine produce laxative effect. Ex: Isapgol*

   (*iii) **Adsorption.** Certain drugs like kaolin adsorb water on to its surface and there by* reduce gastric motility

   (*iv) **Radioactivity.** The radioactive substances are commonly used to treat cancer.*

3. Through Enzymes (Target)

Drugs may either increase or decrease enzymatic reactions.

(*i) Adrenaline stimulates adenyl cyclase*

(*ii) Pyridoxine acts as a cofactor and increases decarboxylase activity*

(*iii) Allopurinol competes with hypoxanthine for xanthine oxidase*

(*iv) Physostigmine and neostigmine compete with acetylcholine for cholinesterase*

- **4. Through Receptors**

  A large number of drugs act through specific macromolecular components of the cell, which regulate critical functions like enzymatic activity, permeability, structural features, template function etc.

2. Chemical Properties

The drugs react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.

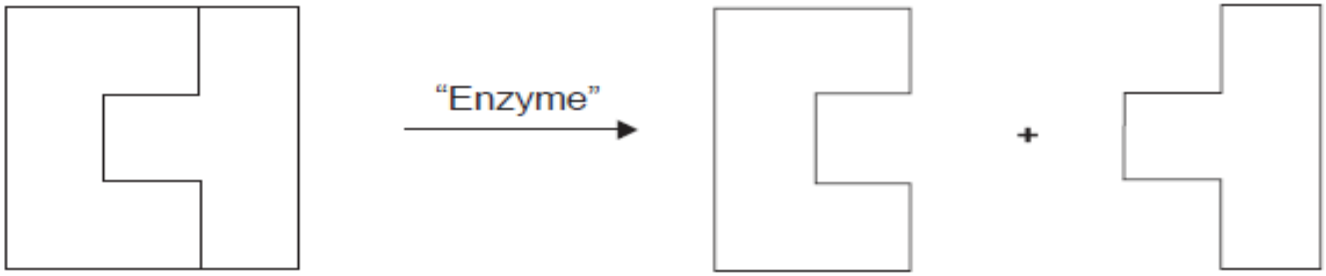
(*i) Aluminium hydroxide neutralizes acid in stomach*

(*ii) Toxic heavy metals can be eliminated by chelating agents like EDTA, BAL,* penicillamine etc.

(*iii) Oxidising agents are germicidal.*

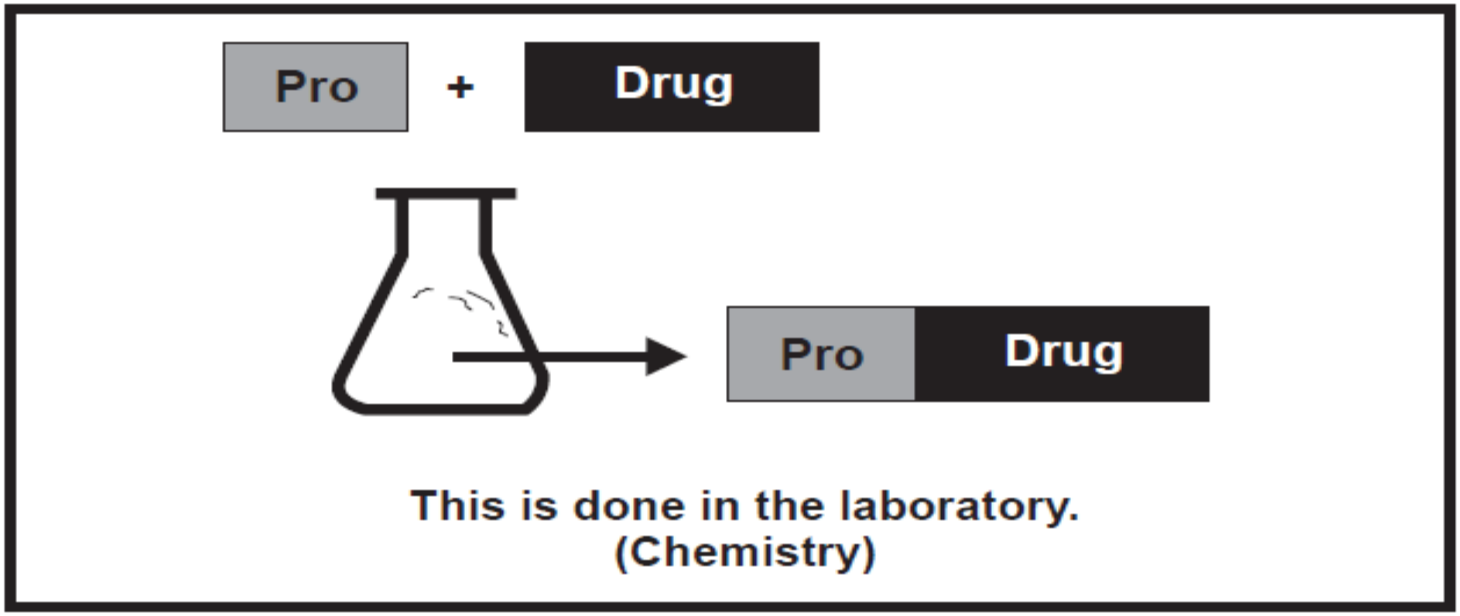
PRODRUG

- Albert in 1958.
- Pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness and/or to decrease associated toxicity.

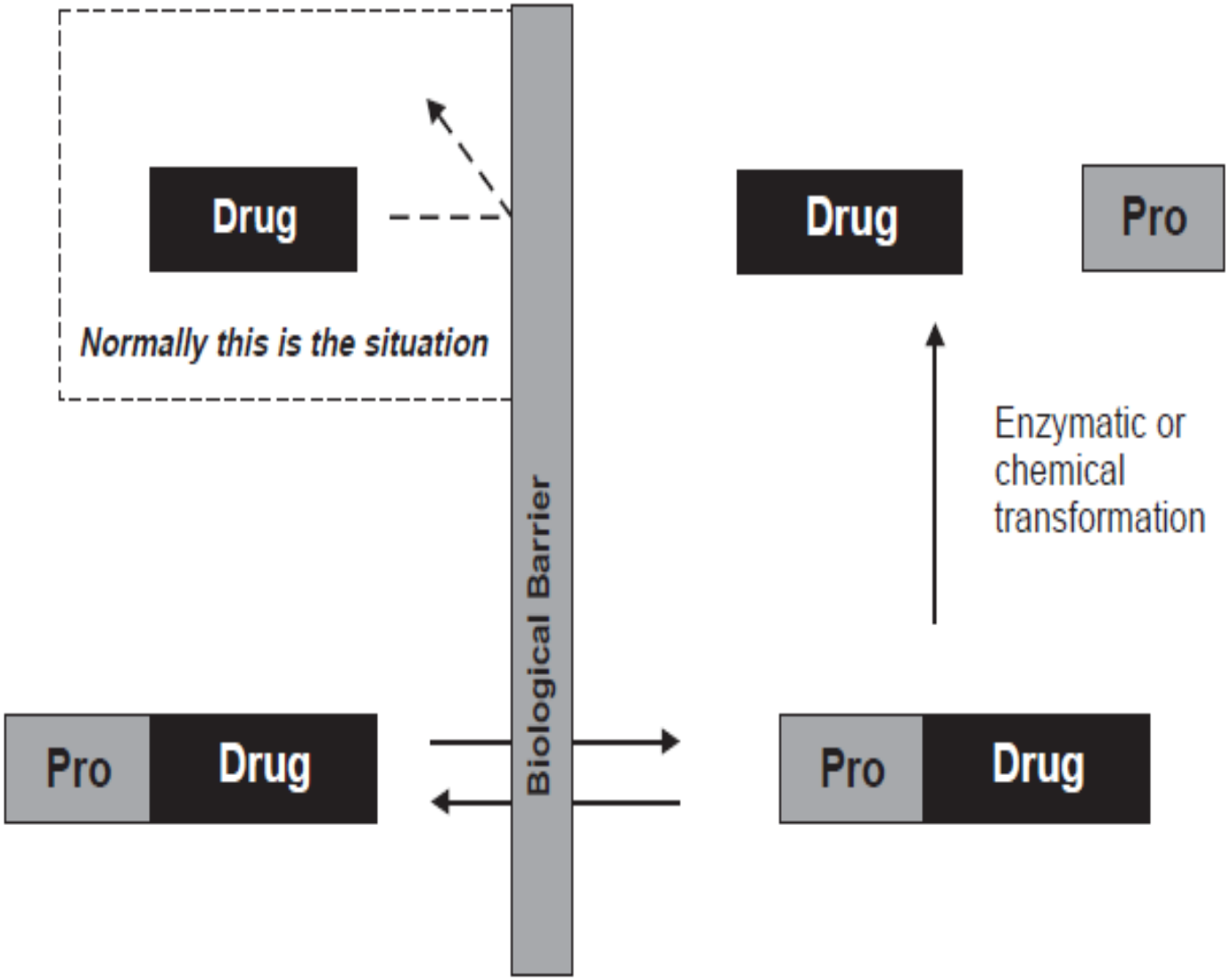


Drug + Cap = Prodrug
(synthesis in the lab)

Drug Cap
(released at the site of action)



This is done in the laboratory.
(Chemistry)



This is happening in the body.
(*In vivo*)

- ‘latentiated drugs’,
- ‘bioreversible derivatives’,
- ‘congeners’.
- Ideally, the prodrug is converted to the original drug as soon as the derivative reaches the site of action, followed by rapidelimination of the released de rivatizing group without causing side effects in the process.

- Prodrugs are pharmacologically inactive derivatives of active drugs.
- They are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug.

Applications

Prodrugs are converted into the active drug within the body through enzymatic or non-enzymatic reactions.

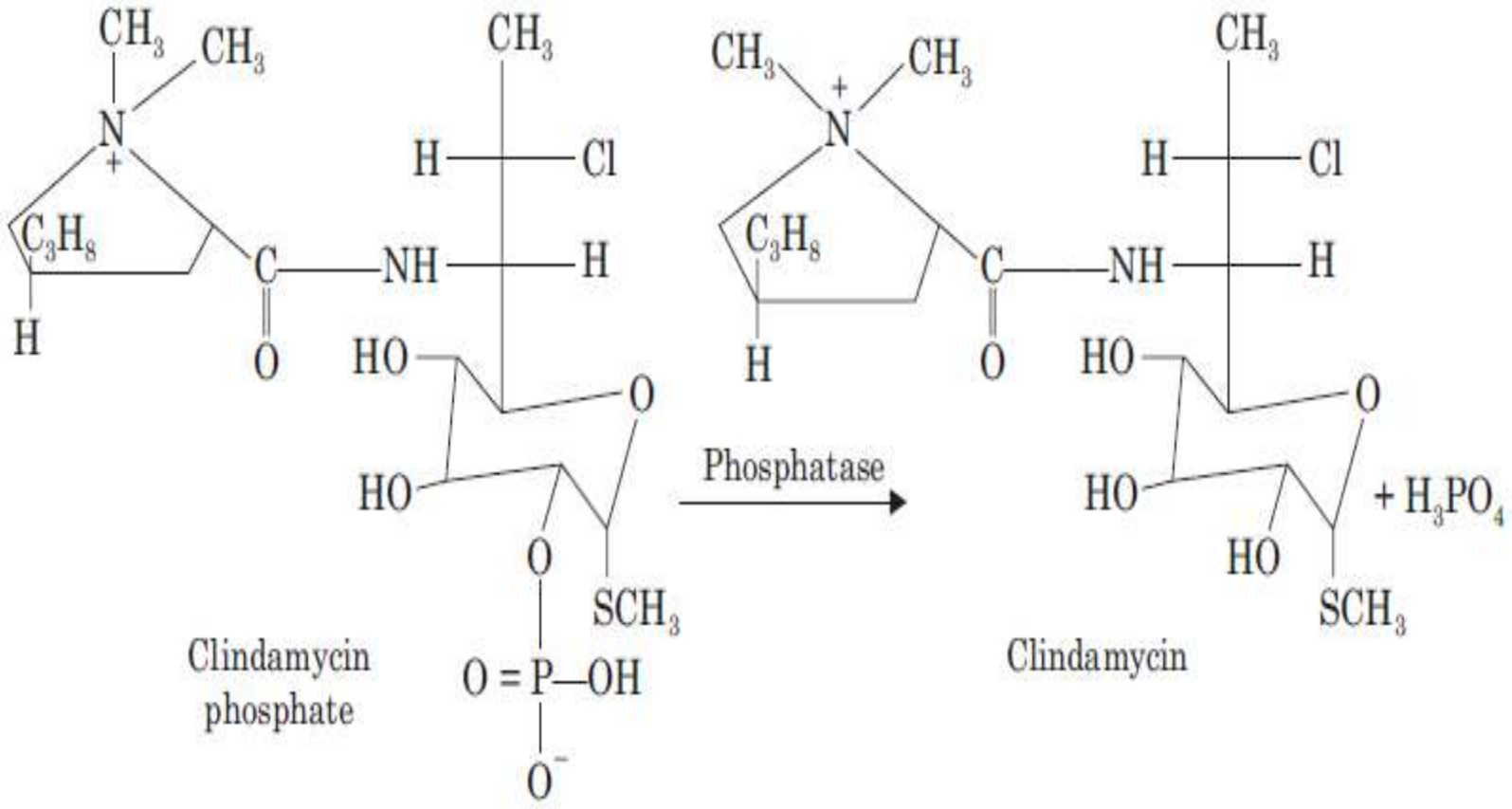
1. Improved physicochemical properties (e.g., better solubility)
2. Enhanced delivery characteristics
3. To improve drug penetration through biological membranes
4. To increase site specificity of the drug
5. To improve the drug's stability and solubility
6. To increase duration of pharmacological activity
7. To decrease the drug's toxicity and adverse effects
8. To improve patient acceptence.

An ideal prodrug must meet the following requirements;

1) The prodrug is inactive or less active than the parent compound
2) The linkage between the drug and the carrier must be cleaved *in vivo*
3) The carrier molecule released *in vivo must be non-toxic*
4) The metabolic fragments of carrier molecule, apart from the drug should be non-toxic

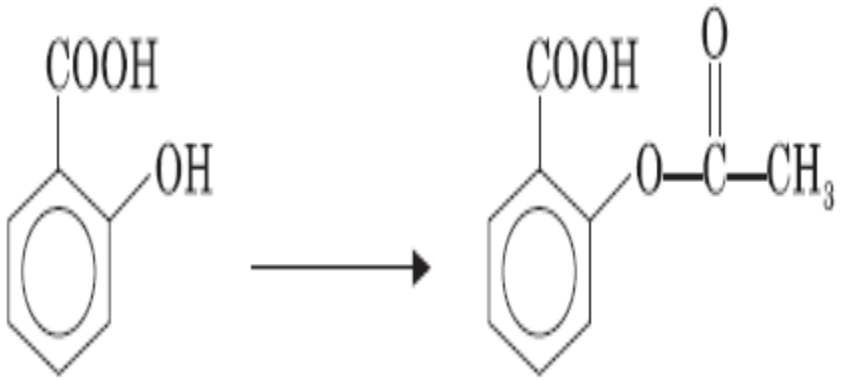
1. **To Improve patient acceptance. One of the reasons for poor patient compliance,**

- Children, is the bitterness- To overcome the bad taste of drug.
- Reduction of drug solubility in saliva
- Lowers the affinity of drug towards taste receptors.
- Ex. : Clindamycin has bitter taste, by increasing the chain-length of 2-acylesters of clindamycin, the taste improved from bitter to non-bitter taste (phosphate ester).


Clindamycin phosphate
Phosphatase
Clindamycin
+ H_3PO_4

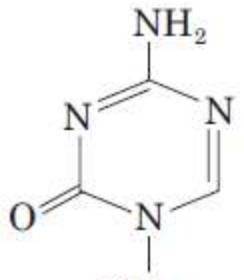
2. To reduce gastric irritation. Several drugs (NSAIDS, nicotinic acid, kanamycin, diethylstilboestrol) cause irritation and damage to gastric mucosa..

Ex. : Salicylic acid to aspirin

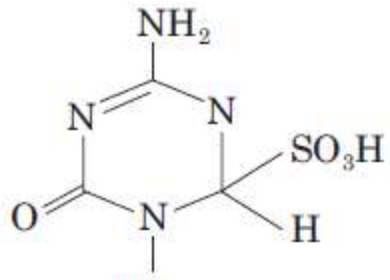


3. **To improve chemical stability. Several drugs may decompose during their shelf** life or in the GIT when used orally.

   Azacytidine (antineoplastic drug) in aqueous solution is readily hydrolyzed but its bisulphite prodrug is stable



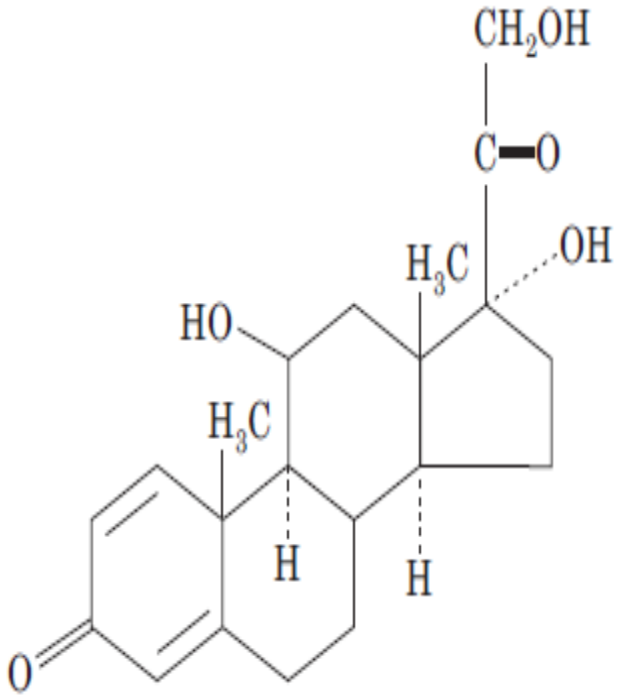
Azacytidine



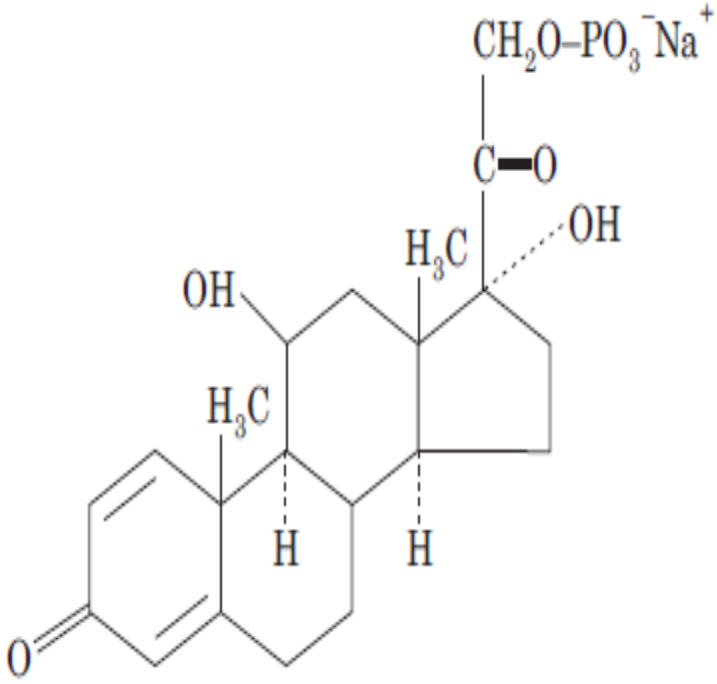
Bisulphite prodrug of azacytidine

4. Prodrugs for increased water solubility.

- **Drugs with hydroxyl functional group** can be converted into their hydrophilic forms by use of half-esters such as hemiglutarates or hemiphthalates ; the other half of these acidic carriers can form sodium, potassium or amine salts and render the moiety water soluble.
- Ex. : Prednisolone and methylprednisolone are poorly water-soluble corticosteroid drugs.
- Prednisolone phosphate is a water-soluble prodrug of prednisolone that is activated *in vivo by* phosphatases.



Prednisolone



Prednisolone sodium phosphate

5. To decrease drug's toxicity and adverse effects. An important objective of drug design is to develop drugs with high activity and low toxicity

Dipivaloylepinephrine prodrug instead of epinephrine to treat glaucoma.

6. To improve membrane transport.

Membrane transportation characteristics of the neurotransmitter dopamine used for the treatment of Parkinson's disease can be improved by administering its prodrug L- 3,4-dihydroxyphenylalanine (Levo-DOPA)

This derivative has better blood-brain permeation characteristics since it uses amino acid channels for transportation.

Once inside the cell, decarboxylase enzyme removes the acid group to generate dopamine.

- **7. Prolonged Activity.**
- **8. Tissue specific prodrug design.**
- **9. Prodrug design based on site specific conditions.**
- **10. Enzyme specific prodrug designs**

Bioavailability (F)

- One of the most commonly used PK parameters for non-IV administered drugs is bioavailability (F).
- It is the fraction of the dose that reaches systemic circulation unchanged.
- Usually, IV administration is considered the 100% control, because drug dosed IV goes immediately into plasma and does not does experience absorption or first-pass effect.

- Two main causes of less than 100% bioavailability are incomplete intestinal absorption and first-pass effect.
- The fraction absorbed can be reduced by processes such as slow dissolution, low solubility, low permeability, and gut efflux transport.
- First-pass effect occurs by way of gut and liver metabolism and biliary clearance during the first pass of these organs.

- Factors that affect absorption or first-pass effect can affect bioavailability.
- For example, absorption of a specific drug can differ among polymorphs, salt forms, formulations, or food effect.
- First-pass effect can vary with metabolic enzyme and efflux transporter expression level, inhibition, induction, and liver disease.

Bioavailability Measure

- The drug is dosed IV, plasma samples are collected and analyzed, and the AUC iv is calculated.
- After a period of compound washout, or using different living subjects, the drug is dosed PO (or whatever non-IV route is of interest), plasma samples are collected and analyzed and the AUC po is calculated.

Bioavailability is calculated from the expression:

$$\%F = (AUC_{PO}/AUC_{IV}) \times (Dose_{IV}/Dose_{PO}) \times 100\%$$

- Goal of at least 20% oral bioavailability for advancement of a candidate to clinical trials.
- Drugs with low oral bioavailability can have significant variability among patients and will require a higher oral dose.

TISSUE CONCENTRATION

- Blood-organ barriers limit penetration into some tissues.
- CNS drugs must penetrate into brain tissue through the BBB
- The penetration of cancer drugs into tumors might be reduced, compared to other tissues, by reduced blood flow, tumor morphology, and efflux transport.

- Total tissue unbound concentration is often measured in drug discovery
- By sampling tissue samples in terminal PK studies
- And Multiplying by the fraction unbound in that tissue.

INTRODUCTION-PK

- After a drug is orally administered, its concentration in the bloodstream and tissues changes with time, first increasing as it enters systemic circulation and then decreasing as it is distributed to tissues, metabolized, and excreted.
- Time course of the drug and metabolite concentrations in the body

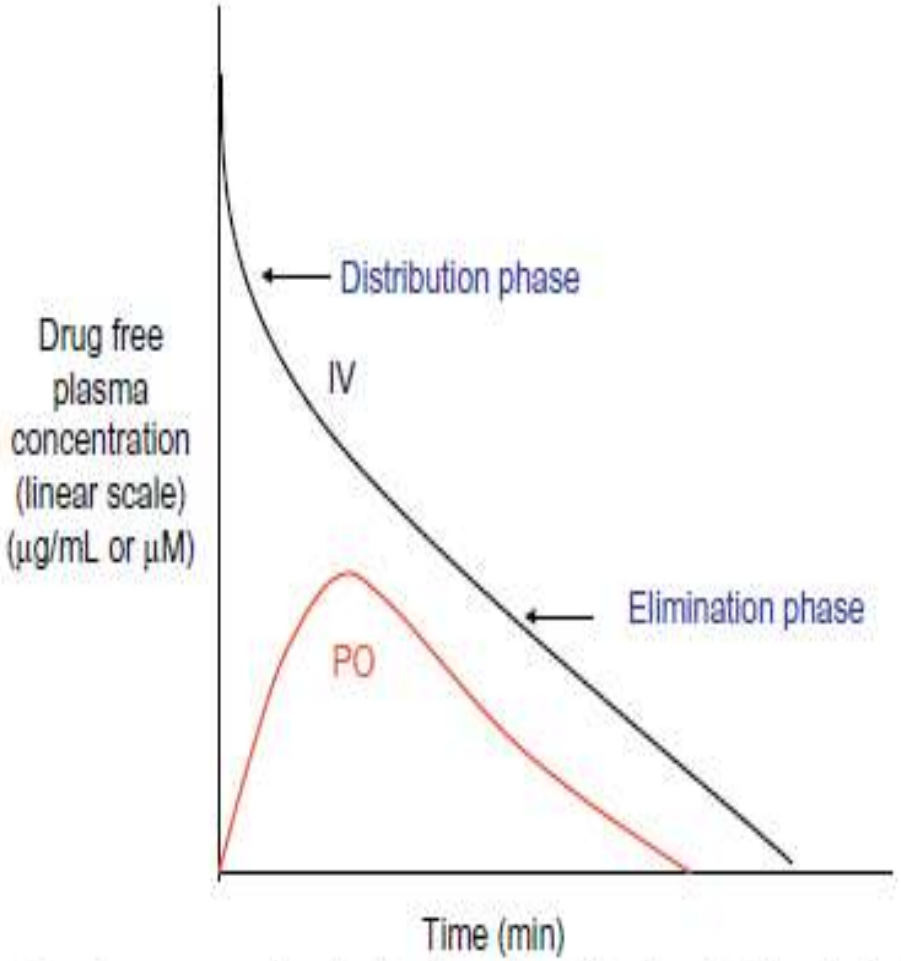
PK

- Blood because it is easy to access in animals and humans, and the unbound drug concentration in the blood is related to the unbound drug concentration in the therapeutic target tissue.
- The unbound drug concentration in the target biophase engages the target to produce the therapeutic effect.

Reasons to Study PK

- In vivo PK is the composite outcome of all the drug properties and in vivo interactions
- Quantitatively measure the in vivo concentration of drug over the time course to obtain insights on the action of the living system on the drug.
- Clearance, half-life, volume of distribution
- Predicts the PK behavior of the drug

- Therapeutic effect might be related
- To a minimum dose or plasma concentration,
- The ratio of in vivo C unbound, blood, max to in vitro IC50 (might define threshold of efficacy),
- How rapidly the C unbound, blood reaches a specific level (might indicate onset speed),
- AUC unbound (might be related to target exposure)
- How long the C unbound stays above a certain C (might relate to duration of action)
- To provide guidance for lead optimization.
- To predict in vivo efficacy and toxicity.



Hypothetical example of free drug concentrations in blood over time following administration by intravenous (IV) and oral (PO) routes.

- When a drug is administered orally, it must first dissolve, permeate through the gastrointestinal membrane, and pass through the liver before reaching systemic circulation.
- As a result, there is a time delay (T max) until the drug reaches its peak concentration in the blood (C max).
- Once it reaches the bloodstream it undergoes distribution to the tissues and excretion, similar to IV dosing.
- Compound exposure is indicated by the area under the time-concentration curve (AUC)

PK PARAMETERS

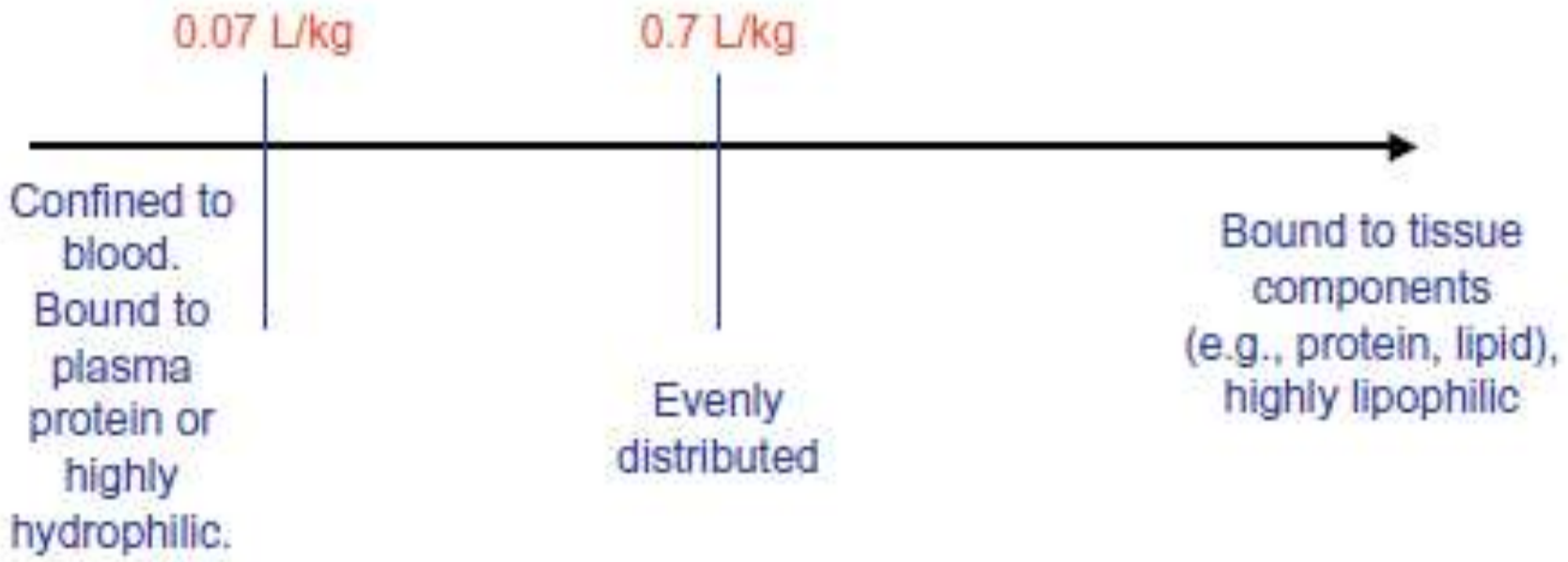
- PK parameters are used in drug discovery, development, and clinical practice.
- It is useful to understand how they relate to the physicochemical, metabolic, and structural properties of the drug.

Volume of Distribution (Vd)

- Volume of distribution (Vd) indicates how the drug distributes between plasma and body tissues

- Vd can be used as a volume (e.g., L), but is more commonly normalized by dividing by the total body weight, thus giving the units L/kg (kg of body weight) or mL/kg.
- Vd is not an actual measurable volume.
- Instead, it represents the apparent total volume into which the drug is distributed, if the concentration in the tissues is the same as the concentration in the plasma.
- Vd is dependent on the drug's physicochemical properties:

- Low Vd drugs are either highly bound to plasma proteins versus tissue components, or not lipophilic enough to bind to tissues.
- Moderate Vd drugs are moderately lipophilic, so they permeate into cells, and are moderately bound to plasma protein and tissue components.
- High Vd drugs are highly permeable into cells and highly bound to tissue components versus plasma proteins. These drugs tend to be highly lipophilic.


0.07 L/kg
0.7 L/kg
Confined to blood. Bound to plasma protein or highly hydrophilic.
Evenly distributed
Bound to tissue components (e.g., protein, lipid), highly lipophilic

The binding of a drug to plasma protein versus tissue components is described by the following expression:

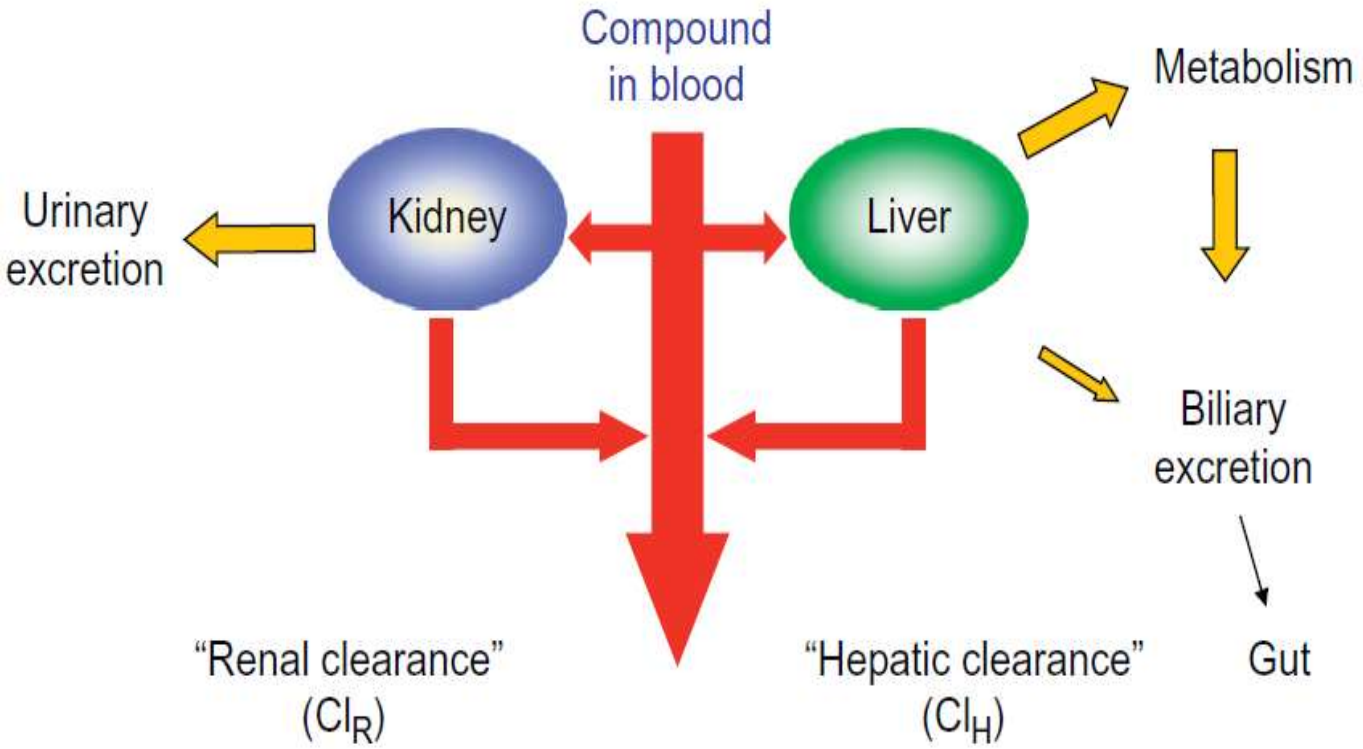
$$V_d = V_{plasma} + V_{tissue} \cdot \left(f_{u,plasma} / f_{u,tissue} \right),$$

where V_{plasma} is plasma volume, V_{tissue} is tissue volume, $f_{u,plasma}$ is fraction of unbound drug in plasma, and $f_{u,tissue}$ is the fraction of unbound drug in tissue. This relationship explains the categories of drugs described above. If a drug is highly bound in plasma proteins, $f_{u,plasma}$ is low and V_{plasma} predominates. If a drug is highly bound in tissue, $f_{u,tissue}$ is low and V_{tissue} predominates. If $f_{u,plasma}$ and $f_{u,tissue}$ are similar, then V_d is the sum of V_{plasma} and V_{tissue}.

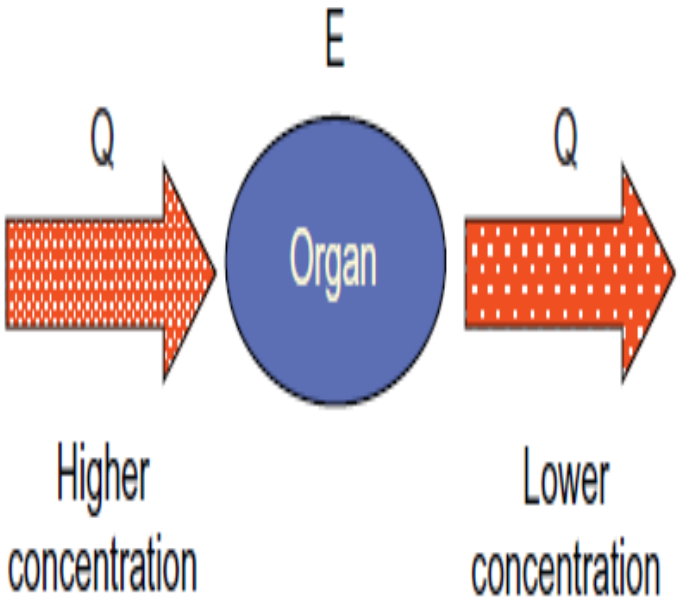
Clearance

- Indicates the rate at which the dosed drug is permanently removed from plasma.
- Due to metabolism, excretion, or chemical degradation.
- Movement into tissues is not clearance, because the drug molecules will later move back into plasma.
- Hepatic, renal, and biliary clearance,
- Liver and kidney.

- Clearance is the volume of plasma from which drug is completely removed in a unit of time.
- mL/min/kg.



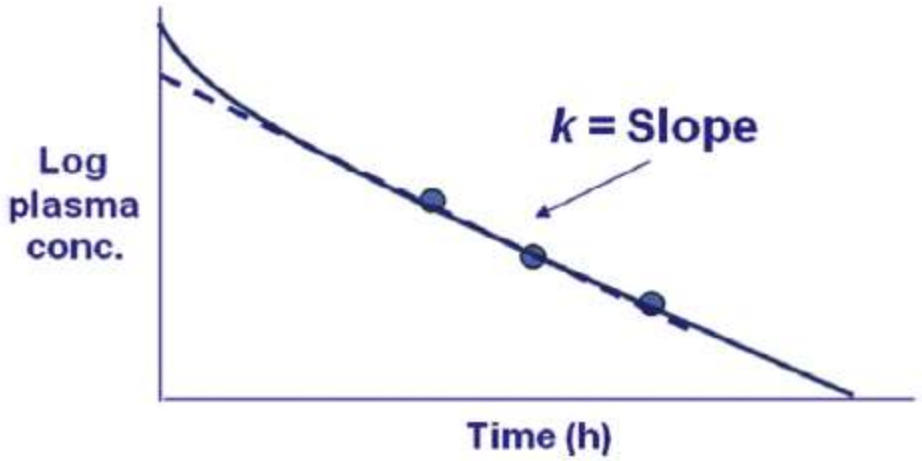
- Systemic clearance (CLS) is used to indicate the total clearance of compound from all sources
- CLS is mostly comprised of CLR and CLH.
- Minor routes of clearance include saliva, sweat, and breath. Metabolism can occur to a lesser extent in tissues and drugs can degrade in blood.
- Clearance by an organ is determined by two factors: blood flow into the organ (Q) and extraction ratio by the organ (E)
- CL=QXE



Extraction of compound by the liver or kidney is dependent on the blood flow to the organ (Q) and the extraction ratio of the organ (E).

Half-Life (t½)

- The time for the concentration of a drug in systemic circulation to reduce by half is termed half-life (t½).
- Drug clearance typically follows first order kinetics, so a plot of log drug concentration versus time provides the elimination rate constant (k) as the slope.
- t½ is calculated from k using the first order kinetics expression: t1⁄2=0.693/k
- t½ can also be calculated from Vd and CL using the expression
- t1⁄2=0.693VdXVd/CL



First order rate constant (k) for elimination is obtained from a plot of log compound concentration versus time.

PK half-life is determined by Vd and CL.

Increasing CL decreases t½, because drug molecules are being removed from the blood at a higher rate.

Increasing Vd increases t½, because tissue is a depot for drug, so a higher Vd increases the amount of drug in tissue that can diffuse back into the blood as drug molecules are removed from the blood.

- One application of half-life is dosing interval
- Regular dosing of a drug product to maintain the in vivo drug plasma concentration
- Re-dosing typically is performed every 1-3 half-lives to maintain the concentration level, thus a human PK t½ of 8-24 h is conducive to once-per-day dosing.

DRUG RELEASE

- The strategies used to control the drug release from pharmaceutical systems are based on biological, physicochemical, and mathematical principles.
- Enhanced product safety,
- Improved patient convenience,
- Achieved by designing, and developing technologies that modify the temporal and spatial drug release profile.

Controlled release systems

- Developed with dependence on the active agent
- Aim to control drug exposure over time,
- Assist the drug in crossing physiological barriers,
- Shield the drug from premature elimination
- Guide the drug to the desired site of action
- Minimizing drug exposure elsewhere
- Patient compliance to the therapeutic increases.

- There are chemical and biological mechanisms to control the drug release spatially.
- Basically, they are dissolution, diffusion, osmosis, partitioning, swelling, erosion, and targeting.

Dissolution

- By which molecules of a solute (such as an active agent) are dissolved in a solvent vehicle.
- The transfer of drug molecules or ions from its solid phase to the surrounding medium (generally water, tissue or, in some cases, polymer).
- The solution is said to be saturated when it contains a solute at the limit of its solubility, considering the conditions of temperature and pressure.
- Supersaturated solutions are characterized to contain the solute in solution above its normal solubility limit.

- The rate at which the drug dissolves from the solid may be used to predict the drug release rate from the therapeutic system.
- The higher the solubility, the more rapid the rate of dissolution when no chemical reaction is involved

- The dissolution process occurs when the solvating medium surrounding a solid drug particle is not saturated and can be controlled by the solvating medium, surface area of the solid, thickness of the boundary layer, and the diffusion coefficient .
- When the solid is placed in contact with the dissolution medium, the surface of solid contacts the medium and the molecules are solvated and removed from the solid.
- The solvated molecules (solute) increase in the medium, increasing the concentration of solute (*Cs).*
- *This increase of solute concentration produces a boundary layer around the solid where the dissolution medium tends to be saturated and the dissolution rate decreases.*

- *The removal of the boundary layer causes the renewing of the solvent, increasing the dissolution rate*
- *Thus, the difference between the solute concentration at the inner portion of the boundary layer (C1) and the outer boundary layer (C2) predicts the dissolution rates.*
- *When the difference is big, the dissolution rate is greater.*
- *when the difference is small, the dissolution rate is lower.*
- *The thickness of the boundary layer (l) is also important and conversely proportional to the dissolution rate*

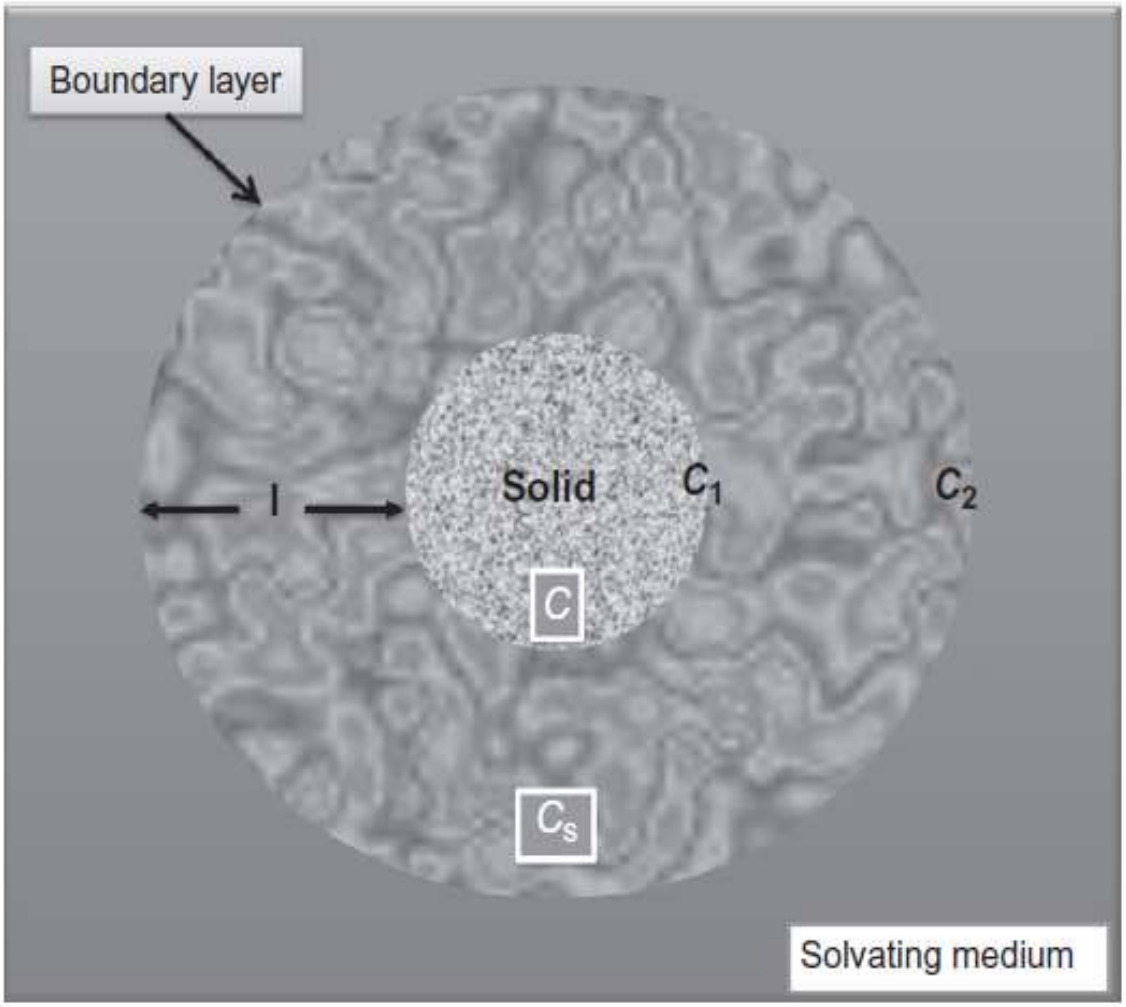


Figure 4.1 Dissolution process and rate: C_s is the concentration of solute; C is the concentration of solid; l is the thickness of the boundary layer; C_1 is the concentration of solute in the inner boundary layer; C_2 is the concentration of solute in the outer boundary layer.

Therefore, the dissolution process is mathematically described as

$$\frac{dC}{dt} = D \cdot A\left(C_s - C\right) \tag{4.1}$$

where the dissolution rate (dC/dt) is dependent on the diffusivity coefficient of solute (D), the surface area of solid (A), and the difference of solid solubility (C) and solute concentration (C_s).

Partitioning

- Delivery systems - different affinities or polarities and leading the active agent to the organism.
- Drug molecules often find an interface between two materials (e.g., hydrophilic and hydrophobic polymers and oils) or phases (e.g., blood, water, and biomembranes).
- This movement of drug molecules from one phase to another is dependent on their relative concentrations (or chemical potentials) and their affinities for each phase.
- This affinity can be measured by the ratio of drug solubilities in the two phases and is defined as partition coefficient

$$P = \frac{C_o}{C_w} P$$

where *Co is the concentration of the drug in the oil or hydrophobic phase and Cw is the concentration in the aqueous or hydrophilic phase.*

- Active agents partitioning between aqueous and lipid biophases, such as drugs of high-lipid solubility, are suitable for entry into the *stratum corneum.*
- *On the other hand, they have poor in-water solubility and their water/lipid partition coefficient is too low.*
- *Thus, they will not partition efficiently into the viable epidermis, and the drugs will be detained in the stratum corneum.*

- It is possible to formulate polymeric systems containing micelles with hydrophobic cores and hydrophilic coronas; hence, they are soluble in the aqueous environment of the organism.
- Hydrophilic drugs will partition in the coronas and hydrophobic drugs will partition in the cores. The first ones are retained for a short period and the second ones are released for extended periods of time.

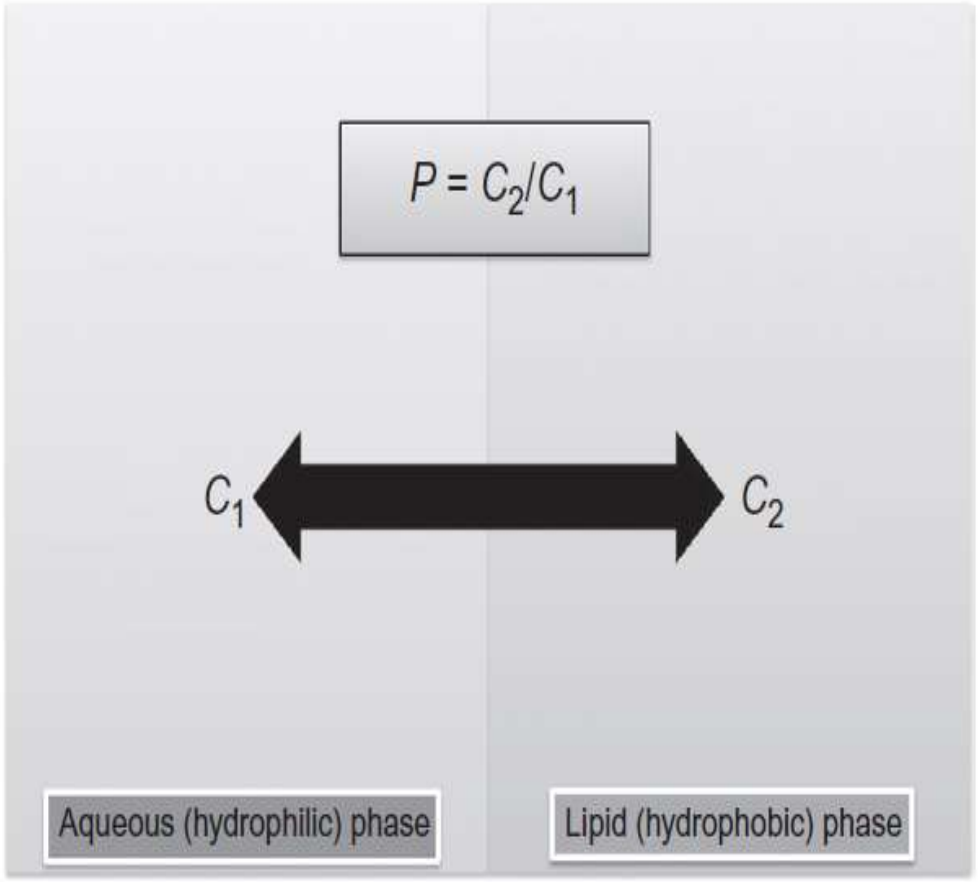


Figure 4.2 Schematic process of drug partitioning: C_1 is the drug concentration in the hydrophilic phase; C_2 is the drug concentration in the hydrophobic phase; P is the partition coefficient.

Diffusion

- The movement of the molecule from one point to another
- The solute will spontaneously diffuse from a region of high concentration to one of low concentration.
- Macroscopically, large number of drug molecules lead them from regions of higher concentration to regions of lower concentration.

- In diffusion, the mass transfer is a kinetic process that occurs in systems that are not in equilibrium.
- The molecular diffusion is driven by the gradient of the solute concentration, considering the solution divided into volume groups with individual solutes, without preference for motion in any particular direction.

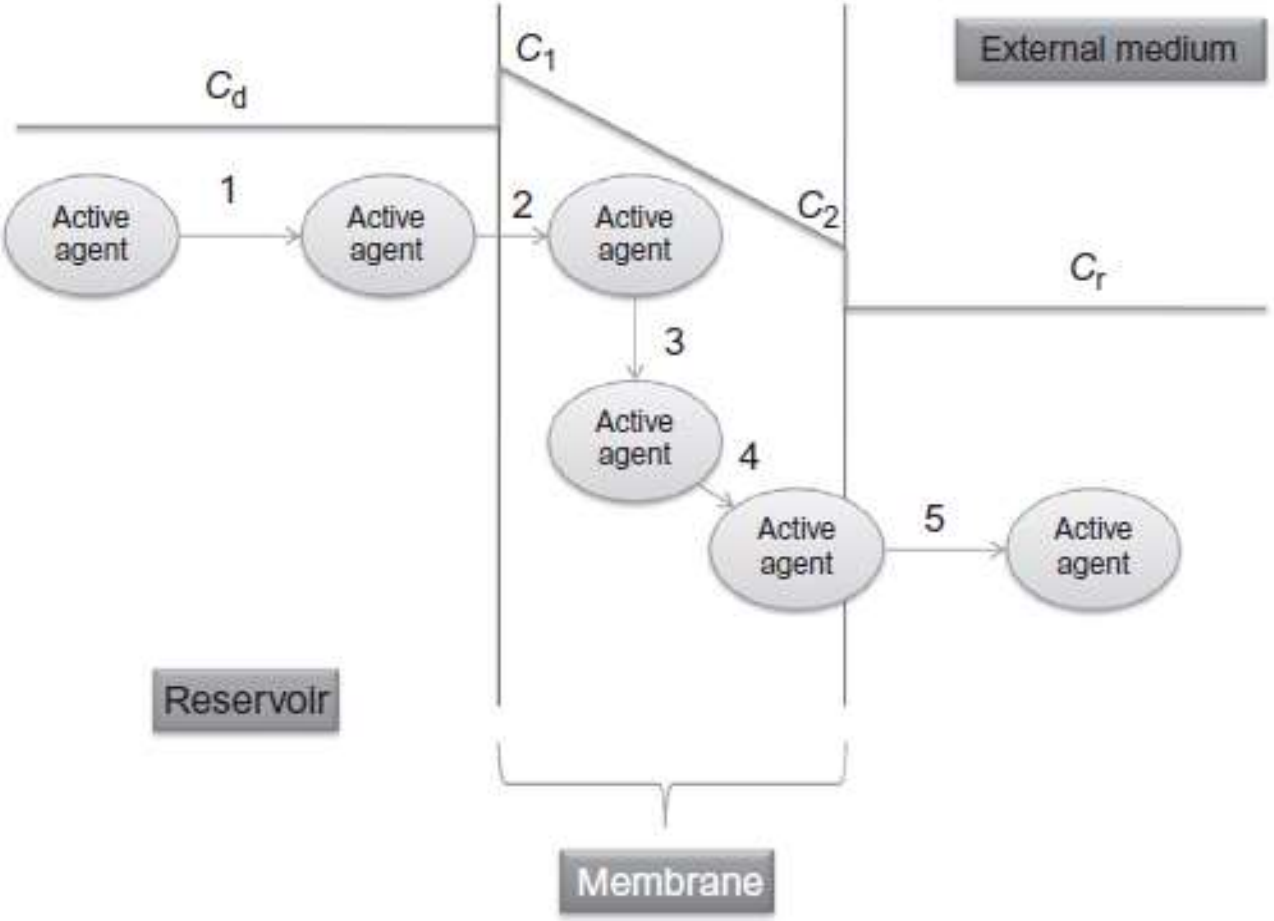


Figure 4.4 Schematic representation of steps of active agent release from a reservoir system: (1) diffusion along the reservoir; (2) dissolution or partitioning between the carrier fluid and the membrane; (3) diffusion through the membrane; (4) partitioning between the membrane and the external fluid medium; (5) transport from the system surface. The concentrations of active agent through the sites are (C_d) reservoir; (C_1) inner membrane; (C_2) outer membrane; (C_r) external medium.

Osmosis

- Solvent is transferred through a semipermeable membrane to dilute a solution containing solute and solvent.
- When two solutions of different concentrations are separated by a semipermeable membrane that is permeable to the smaller solvent molecules but not to the large solute molecules, then the solvent will tend to flow through the semipermeable membrane from the less concentrated to the more concentrated solution.
- It is an effort to equalize concentrations of the impermeable solutes on both sides of the membrane.

- Considering biological organisms, the solvent is water. The transport of water and other molecules across biological membranes is essential to many processes in living organisms.
- Osmotic pressure is the energy that drives the process and controls the drug release from therapeutic systems.

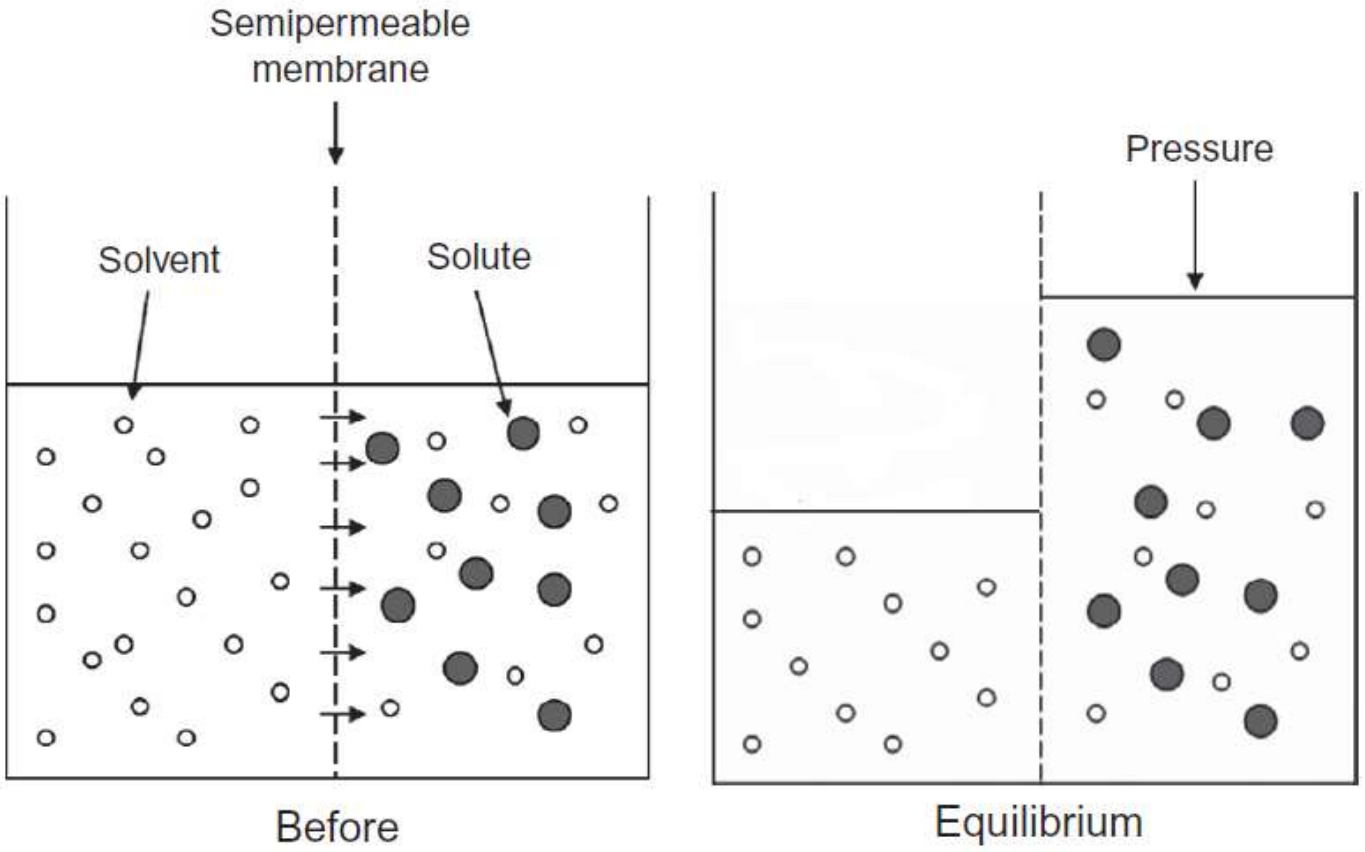


Figure 4.6 Diagram of principle of osmosis.

$$\frac{dV}{dt} = \left(\frac{A}{h}\right) Lp\left(\sigma\Delta\pi - Jp\right) \tag{4.13}$$

where dV/dt is the volume flow of solvent through the membrane, A is the cross-sectional area for transport, h is the membrane thickness, Lp is the hydraulic permeability of the membrane, σ is the reflection coefficient, $\Delta\pi$ is the osmotic pressure difference across the membrane, and Jp is the hydrostatic pressure difference across the membrane.

Swelling

- Characteristics of swelling when in contact with water.
- Hydrophilic behavior and the interaction b/w water and their molecules.
- Polymers are the main materials employed for preparation of controlled drug release systems, and their polymer chains can organize in a three-dimensional fashion.
- When a polymer network is surrounded by water, the network expands and chemical or physical bonds are formed
- This expansion of volume and the consequent emergence of greater spaces between the polymeric chains can be used to control the release of active agents from polymeric systems (matrix or reservoir).

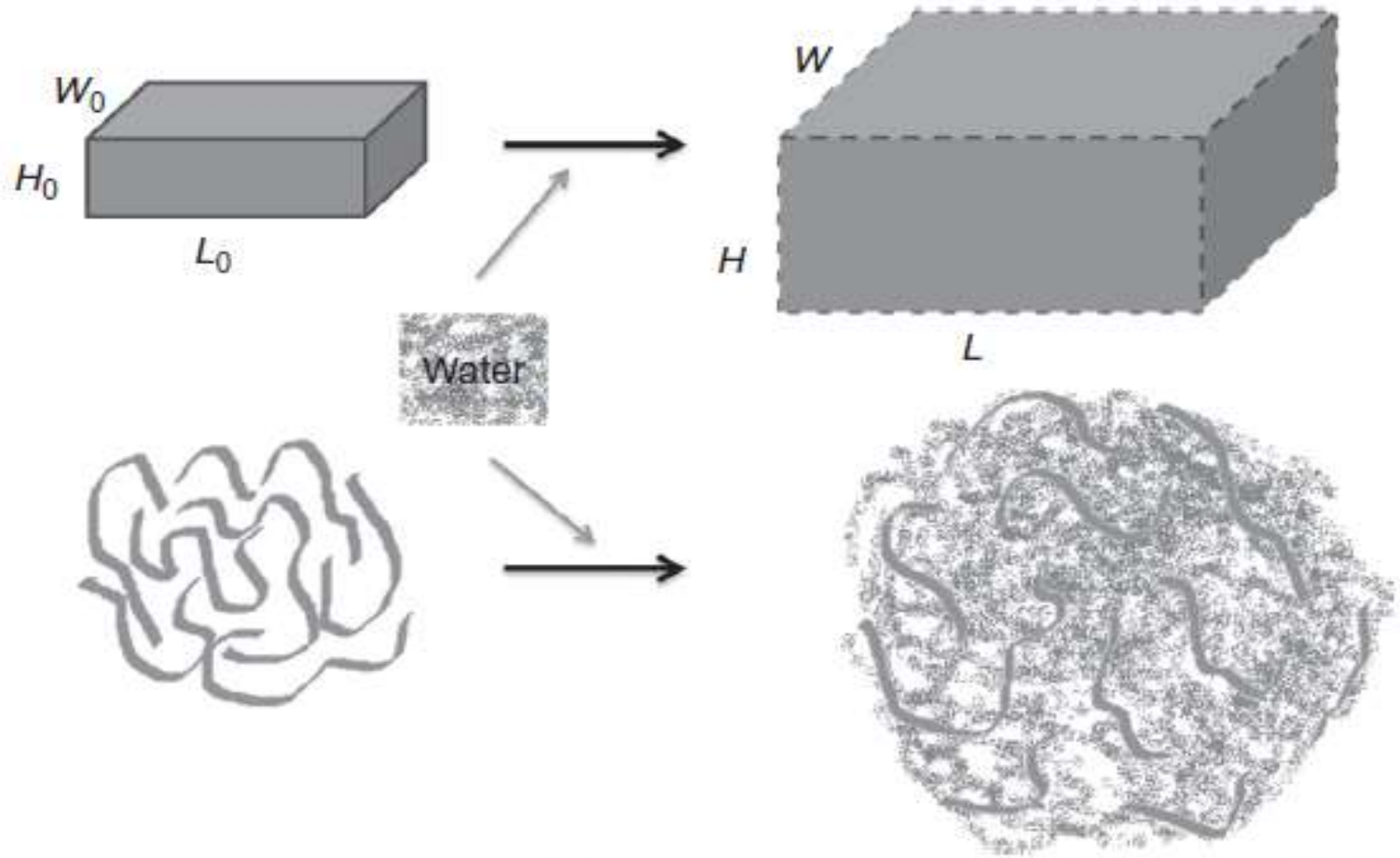


Figure 4.7 Schematic diagram of swelling process: (W_0) initial width; (H_0) initial height; (L_0) initial length; (W) final width; (H) final height; (L) final length.

Erosion

- The polymers used in drug delivery systems controlled by diffusion possess a relatively passive function.
- They are carriers and delay the velocity with which the active agent is distributed to the targeting site.
- Some polymeric carriers are elaborated to play a more active function on the drug delivery process. These polymers suffer erosion when they suffer chemical reactions, releasing the active agent.
- For implantable or injectable therapies, these systems are popular because they do not require retrieval after the active agent is fully released. They are classified into two categories

(1) Systems of physical immobilization

(2) Systems of chemical immobilization

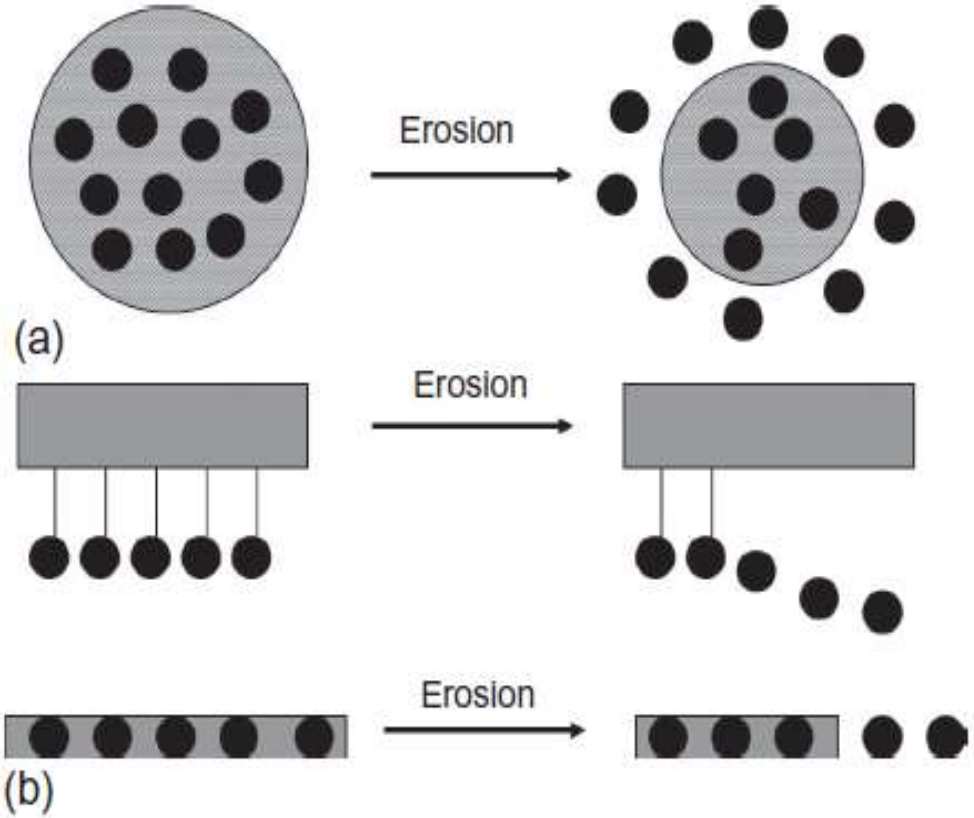


Figure 4.10 Drug delivery systems controlled by erosion: (a) physical immobilization; (b) chemical immobilization.

Drug targeting

- Ability of the active agent to accumulate in the target site selectively and quantitatively, independent of the site and methods of administration.
- The local concentration of the drug at the site(s) should be high, while its concentration in other non-target organs and tissues should be below certain minimal levels to prevent negative side effects.

- *in vivo action of an anticancer drug conjugated to a monoclonal antibody that is specific to a surface antigen on target cancer cells.*
- *Brain to treat Parkinson's, Alzheimer's*
- *Targeting the lung in the treatment of cystic fibrosis*
- *Tissue (e.g., targeting site of inflammation or tumors),*
- *Cellular (e.g., targeting to trastuzumab to human epidermal growth factor receptor-2 and cancer cells),*
- *Subcellular compartment or organelle level (e.g., targeting to cytoplasm, proteins, receptors, mitochondria, DNA and gene therapy applications),*
- *Invading organisms (e.g., targeting viruses, parasites and bacteria),*

Biotransformation

- Chemical alteration of the drug in the body
- Metabolize drugs (essentially foreign substances) have developed to protect the body from ingested toxins.
- Liver; kidney, intestine, lungs and plasma.

INACTIVATION

Most drugs and their active metabolites are rendered inactive or less active

ACTIVE METABOLITE FROM AN ACTIVE DRUG

Many drugs have been found to be partially converted to one or more active metabolite

ACTIVATION OF INACTIVE DRUG

Few drugs are inactive as such and need conversion in the body to one or more active metabolites.(Prodrug)

Metabolism

- Metabolism is the major pathway for the elimination of the majority of xenobiotics and endogenous molecules from the body.
- In the liver, the cytochrome P450 enzymes - role in the metabolism of drugs and have a significant role in "drug interaction" due to enzyme induction and inhibition during multiple drug administration.

Usually, the drug or any xenobiotic undergoes phase I metabolism wherein the toxic compound is structurally converted to non-toxic compound followed by phase II wherein modified metabolite is conjugated with endogenous molecules to make it water soluble for ease of excretion.

NONSYNTHETIC/ PHASE 1

(Oxidation, Reduction, Hydrolysis, Cyclization, Decyclization)

SYNTHETIC/ CONJUGATION/ PHASE II

(Glucuronide conjugation, Acetylation, Methylation, Sulfate conjugation, Glycine conjugation, Glutathione conjugation, Ribonucleoside/nucleotide synthesis)

Phase I - non-synthetic or functionalization reaction

- New functional groups (like –OH, –C=O, or –NH2) are created in the parent molecule so that the functional group can be attached with additional molecules in further steps.
- The metabolite generated may be inactive or active in this phase.
- Only a little effect will be seen in the water solubility of the molecule after phase I biotransformation, but a dramatic effect will be observed in its biological activity

Phase II is also called as synthetic or conjugation reaction

- Molecular groups like alkyl, aryl, various amino acids, and glucuronyl are attached to the phase I metabolite in order to make it water soluble.
- Metabolite generated in this phase is mostly inactive.

Oxidative reactions

- They involve enzymes like CYP450 inside the microsomes and enzymes like MAO, xanthine oxidase (XO) outside the microsomes
- In oxidative reactions, one molecule of oxygen is inserted into the chemical structure with or without the removal of hydrogen molecule from the parent molecule.

- Hydroxylation (R–H to R–OH),
- Dehydrogenation (R–C–OH to R–C=O),
- Deamination (R–C–NH2 to R–C=O),
- Dealkylation (R–CH3 to R–H),
- Carboxylation (R– C=O to R-COOH),
- S-oxidation, and N-oxidation

Reduction Reactions

- Dehydroxylation (R-OH to R-H),
- Hydrogenation (R-C=O to R-C-OH),
- Decarboxylation (R-COOH to R-C=O),
- Amination (R-NO2 to R-NH2),
- Methylation (R-C-H to R-CH3).
- P-nitro benzoic acid ➔nitro-reductase ➔p-aminobenzoic acid (amination)
- Chloramphenicol ➔nitro-reductase ➔ amine of chloramphenicol (amination)

Hydrolysis

- Drugs with esters and amides in their structure undergo cleavage metabolism
- Enzymes like pseudocholinesterase, arylcarboxylesterase, liver microsomal carboxylesterase, and paraoxonase
- Procaine, succinylcholine, procainamide, aspirin, and enalapril.

Cyclization

- The drug with a straight-chain structure is converted to a ring structure.
- Proguanil ➔CYP2C19 ➔ cycloguanil

Phase II Reactions

- Phase II reactions utilize mainly “transferase” enzymes in order to transfer polar molecules to a functional group created in phase I reaction.
- Increasing the polarity of the drug metabolites in phase II results in poor cellular diffusion and low affinity for the receptor.
- Metabolites of phase II often are biologically inactive.

Glucuronidation

- The glucuronic acid is highly available in the liver, and many functional groups like alcohol, phenol, amine, and carboxylic acids undergo glucuronic acid conjugation.
- Glucuronidation is mediated by uridine diphosphate-glucuronosyl transferase (UGT), and in humans UGT1 and UGT2,
- UGT is present in the intestine, lung, nasal mucosa, brain, and kidneys

- Drugs conjugated with glucuronic acid are excreted in bile which then can undergo significant “enterohepatic circulation” after deconjugation by the gut microbes.
- Acetaminophen and morphine

  (O-glucuronidation)
- Ibuprofen (acyl glucuronidation)

Sulfation

- Enzyme sulfotransferase (SULT)
- Endogenous compounds like steroids, catecholamines, thyroxine, and bile acids
- Drugs with phenol moiety readily undergo sulfonation.
- SULT1 and SULT2

Acetaminophen ➔SULT1AI➔ acetaminophen sulfate

Acetylation

- Acetyl CoA can be transferred to the primary aliphatic amines, aromatic amines, and hydrazines in the structure of drug metabolites.
- N-acetyltransferase (NAT) is the enzyme responsible for acetylation reaction.
- Hydralazine ➔NAT ➔hydralazine acetone hydrazine

Methylation

- O-Methyl metabolites formed by this reaction in some cases have higher lipophilicity and increased biological activity.
- Methyltransferase (MT) is the enzyme involved, and it requires S-adenosyl methionine as a cofactor.
- Norepinephrine → COMT →epinephrine (active metabolite) Methylation

Glutathionylation

- Glutathione S-transferase (GST) mediates this reaction and utilizes glutathione as a substrate.

Glycine Conjugation

- Glycine N-acyl transferase (GLYAT)

Microsomal enzymes

- These are located on smooth endoplasmic reticulum primarily in liver, also in kidney, intestinal mucosa and lungs.
- The monooxygenases, cytochrome P450, UGTs, etc. are microsomal enzymes.
- They catalyse most of the oxidations, reductions, hydrolysis and glucuronide conjugation.
- Microsomal enzymes are inducible by drugs, certain dietary constituents, and other agencies.

Nonmicrosomal enzymes

- These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma.
- The esterases, amidases, some flavoprotein oxidases and most conjugases
- Reactions catalysed are: Oxidations and reductions, hydrolytic reactions and all conjugations except glucuronidation

Microsomal Enzyme Induction

- Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and UGTs.
- As a result the rate of metabolism of inducing drug itself (autoinduction) and/or some other co-administered drugs is accelerated

First-pass (Presystemic) Metabolism

- This refers to metabolism of a drug during its passage from the site of absorption into the systemic circulation.
- The hepatic extraction ratio ($_{ER}$liver) of a drug is the fraction of the absorbed drug prevented by the liver from reaching systemic circulation

Specificity

- Measure of a receptor's ability to respond to a single ligand.
- Low specificity - not targeted or intended by drug; side effects
- A classic example is sildenafil which was developed to treat hypertension and angina.
- Observed side effect became the new targeted role of the drug.

Selectivity

- Ability of the receptor to distinguish between drugs
- Adenosine is nonselective (4 adenosine receptors with different actions) and as a result has the unwanted effect of potential
- bronchospasm (A1 receptor), whereas regadenoson is selective for the A2A receptor (vasodilation and bronchodilation).

Affinity

- Strength of attraction between the drug and its receptor.
- A high affinity is generally associated with a lower dose requirement (compared with low affinity for the same receptor).

Potency

- Potency describes the relationship between the drug dose and the magnitude of the effect
- High potency induces a strong effect with a low drug dose.

Efficacy

- Efficacy is the in vivo potency, or the maximum response achieved from a drug
- The interaction (e.g., absorption, metabolism, and excretion) of the drug in the body may alter the relative bioavailability and, thus, change the theoretic effect of the drug.
- Rapid metabolism of a high-potency drug, for example, may render it of low efficacy
- whereas rapid absorption, minimal first-pass metabolism, and delayed excretion may create higher efficacy despite much lower potency

Ideal drug

- Easy to administer, fully absorbed, not plasma bound, of rapid onset, spontaneously eliminated, chemically stable, highly selective and specific, and of high affinity, potency, and efficacy.
- It will also have a useful duration of action, a high therapeutic index (no adverse effects), and no interactions.

- No examples of synthetic or natural drugs that satisfy all these criteria
- For example, high affinity can also cause a prolonged action that may not be desirable.

DRUG–RECEPTOR INTERACTIONS

- Receptors are generally proteins, protein structure
- Ion channels, enzymes, and transporters
- Cells produce proteins with different properties and activities by joining the 20 amino acids into many different combinations and sequences.
- The properties of proteins - physical and chemical properties of the amino acids.
- Proteins can be large molecules with complex 3-dimensional shapes and structures
- Primary, secondary, tertiary, and quaternary structures.

- The primary structure - protein configuration associated with the amino acid sequence: the order of amino acids in the polypeptide chain (peptide bonds).
- The secondary structure - the polypeptide chain is folded (hydrogen bonds), creating pleated sheets and helices.
- The tertiary structure - interactions between amino acid side chains (hydrogen bonds, disulphide binds, ionic binds, and hydrophobic interactions).
- The quaternary structure - interactions between different polypeptide

- When a drug binds to a target, it may regulate the receptor as an agonist or antagonist, or act as an inducer or inhibitor in the case of an enzyme.
- The lock and key chemical and structural interaction is prior to achieving a potent and safe drug.

- PD is the study to determine dose–response effects.
- Effects of a drug on some particular response, such as heart rate, enzyme levels, antibodies production, or muscle relaxation or contraction.
- When a drug binds to a receptor, the ensuing response is complex.

- The response may be local or via a signal transduction process.
- The rate for the forward reaction of drug binding to receptor is proportional to the concentrations of both the drug and the receptor.
- Conversely, the rate for the reverse reaction, that is, dissociation of the drug–receptor complex, is proportional to the concentration of the drug–receptor complex.

- At equilibrium, both forward and reverse reactions are equal.

Mathematically, we have:

- $k1[D][R] = k{-}1[D * R]$
- where *k1 is the forward reaction rate constant, k−1 is the reverse reaction rate constant,*

Rearranging Equation ,

- $[D][R]/[D * R] = k{-}1/k1 = KD$
- where *KD is the equilibrium dissociation constant.*

- When half the receptors are bound
- If we consider all the available receptors as 100% and [D*R] are the occupied receptors
- with drug at the binding sites, then [R] – which is the percentage of free, unoccupied receptors – can be substituted with 100–[D*R].
- **[D] = *KD[D ∗ R]/* 100 – [D ∗ R]**

- LD50 is the lethal dose for 50% of the population,
- ED50 is the effective dose for 50% of the population.
- The lower the ED50 compared to the LD50 the higher the therapeutic index of the drug.
- ***Safety Margin:*** *This is the separation of two doses: one that produces therapeutic* effects and one that elicits adverse reaction.
- The standard safety margin (SSM)
- SSM = LD1 – ED99\ED99× 100
- where LD1 is the lethal dose for 1% of the population
- ED99 is the effective dose for 99% of the population.
- A large safety margin is achieved when there is a significant difference between the ED99 and LD1 doses.

- In drug–receptor binding, the rate at which the association between drug and receptor occurs relative to the rate of dissociation will define the affinity, or the strength of attraction.
- Low affinity, and thus higher dose requirements, is associated with drugs for which the rate of dissociation is appreciably higher than the rate of association.
- High-affinity drugs requiring lower doses for effect tend to be associated with a rate of association well in excess of the rate of dissociation.
- The dissociation constant, which is simply the ratio of the rate of association to the rate of dissociation (smaller means higher affinity), provides insight into both the drug effect and the half-maximal effect.

Pharmacodynamic concepts

- Dose response
- Slope of the curve
- Maximal effect
- Potency and efficacy
- 50% effective dose,
- 50% lethal dose,
- Therapeutic window
- Therapeutic index
- Tolerance
- Sensitization

DRUG INTERACTIONS

- Drug interactions can cause harm
- Increased drug effect (leading to toxicity)
- Decreased drug effect (leading to therapeutic failure)

Synthesis of Inorganic Pharmaceuticals

- Metalions perform crucial functions in biology, but they are widely used for diagnostic and therapeutic agents applications.
- Gadolinium complexes as MRI contrast agents, technetium-99mcomplexes as imaging agents
- Platinum-based anticancer agents drugs.

- Metals - periodic table were designed and developed for a range of diseases
- Cancer (e.g., Ru, Gd, Ti, Ge, V, and, Ga)
- Diabetes (V and Cr)
- Infectious diseases (Ag, Cu, and Ru).
- Each metal has unique features such as redox potentials and ligand exchange kinetics.

- Molecularly targeted drugs- side effects and toxicity of
- Anticancer agents- Targeted drugs - bind to the receptors- overexpressed on the surface of cancer cells
- Epidermal growth factor receptor (EGFR), overexpressed in various tumors
- Functionalized PtII terpyridine complexes with EGFR inhibiting 4-anilinoquinazoline derivatives
- Multiple modes of DNA interaction and were highly potent EGFR inhibitors.

Metalloenzymes

- Metal complexes as enzyme inhibitors is their ability to construct three-dimensional shapes for fine-tuning the optimized enzyme-binding affinity and selectivity.
- Synthesis of half-sandwich IrIII N-heterocyclic carbene (NHC) complexes using pentamethylcyclopentadienyl derivatives as arene co-ligands.
- Antitumor properties against A549 and influenced the mitochondrial membrane potential.

- Characteristics of AD is the formation of extracellular aggregates of the amyloid-beta (Ab) peptide.
- RuIII complexes in which the imidazole ligand was replaced by pyridine derivatives.
- The complexes bind covalently to the Ab peptide.
- Peptide alone leads to precipitation, however, the binding of RuIII complexes causes the formation of soluble high molecular weight aggregates.
- The Ab aggregation was not dependent on the size of the pyridine ligand.
- RuIII complexes were capable of modulating Ab peptide aggregation.

Organic synthesis

- The art and science of replicating the molecules of living nature and creating
- Art and science of constructing Drug in the laboratory substances, natural or designed, whose primary element is carbon

- German chemist Friedrich Wöhler, a Foreign Member of the Royal Society (ForMemRS), synthesized urea, an example of a naturally occurring substance from the living world

- Human hormones such as the steroids and the eicosanoids
- Prostaglandins, thromboxanes and leukotrienes
- Penicillin as a life-saving antibiotic

- Introduction of the theory of retrosynthetic analysis
- Development of several new synthetic methods, reagents and catalysts and the total synthesis of numerous bioactive naturally occurring substances,
- Prostaglandins, leukotriene and macrolide classes, ginkgolide B, maytansine and ecteinascidin.
- Corey was awarded the Nobel Prize in Chemistry in 1990 ‘for his development of the theory and methodology of organic synthesis’

- Alkaloid natural products were synthesized, including tropinone, quinine, morphine and strychnine.
- The total synthesis of strychnine was accomplished by American chemist Robert Burns Woodward
- 1950s and 1960s that culminated in his recognition by the Royal Swedish Academy of Sciences with the 1965 Nobel Prize in Chemistry ‘for his achievements in the art of organic synthesis’

- Calicheamicin cytotoxic properties
- Isolated from *Micromonospora echinospora ssp. calichensis in the 1980s,*
- New synthetic methods and strategies, designed analogues of calicheamicin that exhibit similar biological properties

Pharmacophore

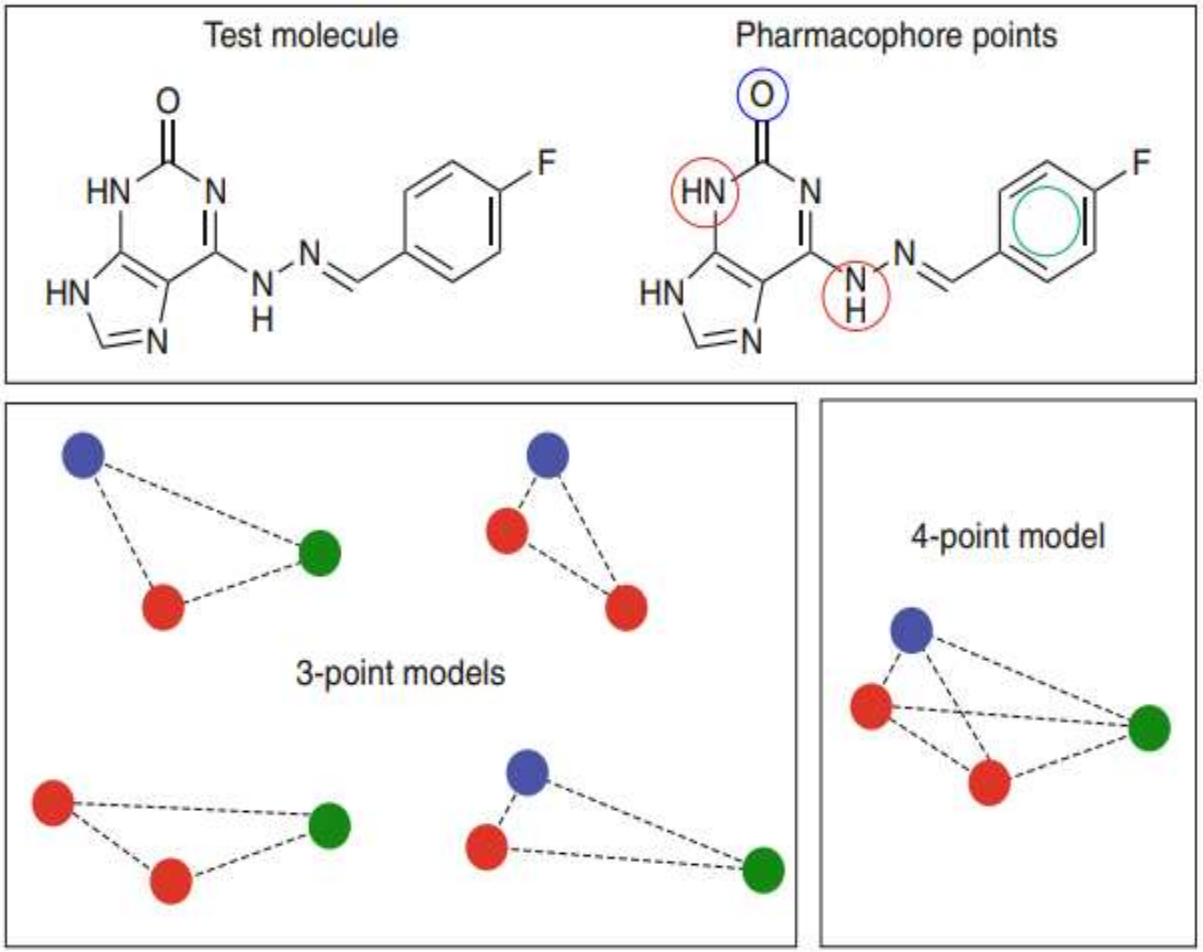
- As the arrangement of those substructures or functional groups in an active compound that are crucial for its activity.
- Pharmacophores can be derived from two- or three-dimensional (2D, 3D) molecular representations, but 3D pharmacophores are most popular (considering the fact that molecules are active in three dimensions).

- A Pharmacophore is an ensemble of steric, electrostatic and hydrophobic properties which is essential for optimal supramolecular interactions with a biolocial receptor, to modulate or inhibit a biological effect.
- A Pharmacophore does not represent a concrete molecule, but an abstract concept which describes the common molecular properties of interaction with the receptor.

- The Pharmacophore anchors the agent with the receptor.
- With pharmacophoric models one can define special properties (pharmacophoric points) based on the structure of the receptor or based on the structure of a known agent.
- This pharmacophoric points can be checked against a database of pharmacophores.

Pharmacophore.

Fig. 1 Model pharmacophore. For an arbitrary test molecule, pharmacophore points and features are assigned (*red* hydrogen bond donor, *blue* hydrogen bond acceptor, *green* aromatic center) and potential three-point pharmacophores combining these features and the corresponding four-point pharmacophore model are shown. *Dashed lines* are inter-feature distances



- An important advancement of the pharmacophore concept
- Transition from an atom-centric representation to pharmacophoric functions.
- This means that important atoms or groups are replaced with different “features,” which represent functionalities important for binding

Pharmacophore features include

- hydrogen bond acceptors (e.g., hydroxyl or carbonyl groups)
- hydrogen bond donors (e.g., hydroxyl or amide groups)
- positively charged (e.g., guanidines)
- negatively charged groups (e.g., carboxylates),
- hydrophobic (e.g., cyclohexyl or isopropyl groups)
- aromatic moieties (e.g., phenyl ring or other aromatic ring systems)

- Features are represented as points;
- For five- or six-membered rings, the centroid position is used as a point.
- Feature points are separated by inter feature distances, which represent the second major component of pharmacophore models.
- The combination of features and inter-feature distances captures the chemical nature of a pharmacophore and its **geometric arrangement**.

- First, only a few parts or functional groups of a small molecule and the interactions they form determine binding and biological specificity.
- Second, from a practical point of view, a systematic evaluation of potential pharmacophore patterns is currently computationally infeasible for pharmacophores containing more than four feature points and increasing numbers of inter-feature distances

- Major applications of pharmacophore models include 3D database searching, the design of active compounds and target-focused libraries (▶ Combinatorial Libraries), and the derivation of models for 3D-QSAR

- Pharmacophore models have increasingly been used to design combinatorial libraries that are focused on biological target families.
- Among others, important target families for pharmacophore-based library design include G-protein-coupled receptors (▶ G-Proteins, ▶ GPCRs) and protein kinases (▶ Tyrosine Kinase).

Characterization:

- (1) Location of the functional groups (e.g. proton donor/acceptor, hydrophobic parts)
- (2) Stabilization of the most effective conformation
- (3) Lipinski's rule of five:

These properties are essential for good permeation

- The molecule has less than five proton-donators
- The molecular weight is smaller than 500 Dalton
- log P smaller than 5
- Molecule has less acceptors than 10

  The molecule should use biological transporters otherwise the ligand is attached too strong or it can not be transported.
- Minimum of pharmacophoric points: 3

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.