

## Pharmaceutical chemistry

3 stage

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Reff. Wilson & Gisv “ text book of organic medicinal a pharmaceutical chemistry”

# Physicochemical Properties in Relation to Biological Action

The influence of the organic functional grps.

Within a drug molecule in :

- (in water, in lipid) solubility.

- steric factor.

- acid-base solubility.

- PC

- stereochemistry.

They are 2 approaches for drug design.

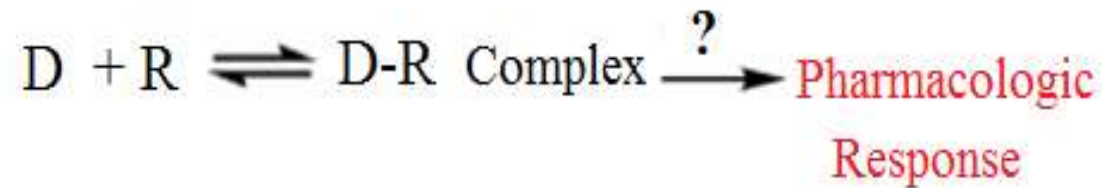
1. classical approach ?

2. modern drug design (approach)(rational appro.) ?

Computerized conformational analysis permits the medicinal chemist to predict the drug's 3D shape that is seen by the receptor.

a good understanding of how drug is transported, distributed, metabolized & excreted

-Drug is a chemical molecule



The ideal drug molecule will show favorable binding characteristics to the receptor, and the equilibrium will lie to the right.

## Drug should be:

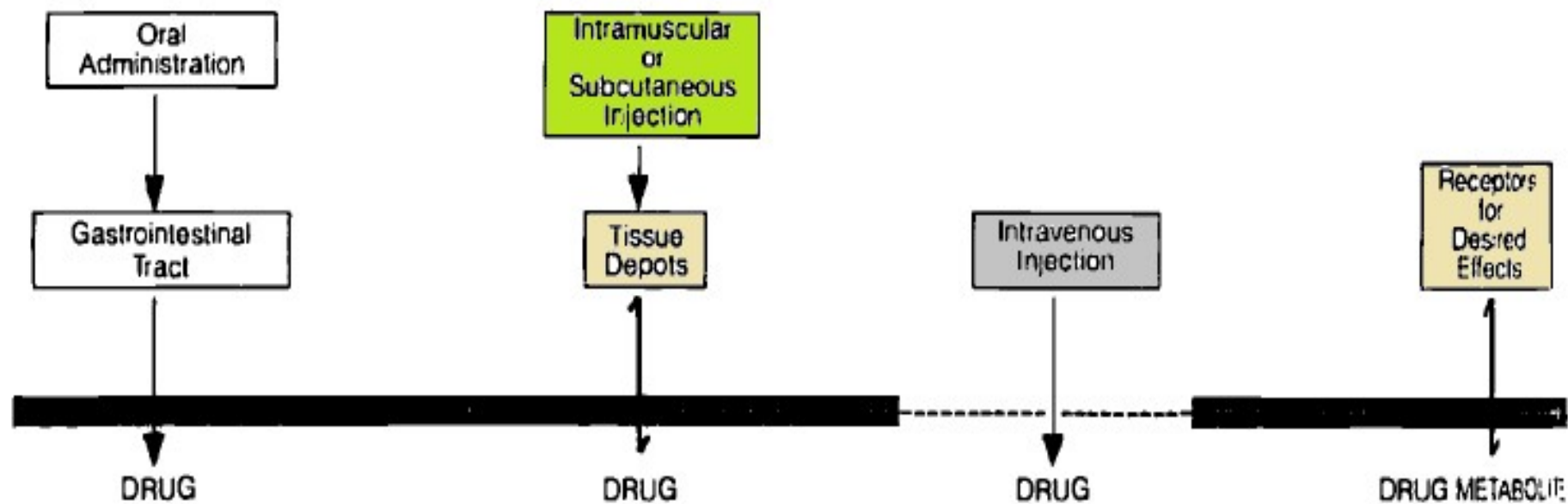
- high affinity for Rec.
- high efficacy.
- should be reversible ,dissociate from the receptor and re-enter the systemic circulation to be excreted

## Major exceptions include :

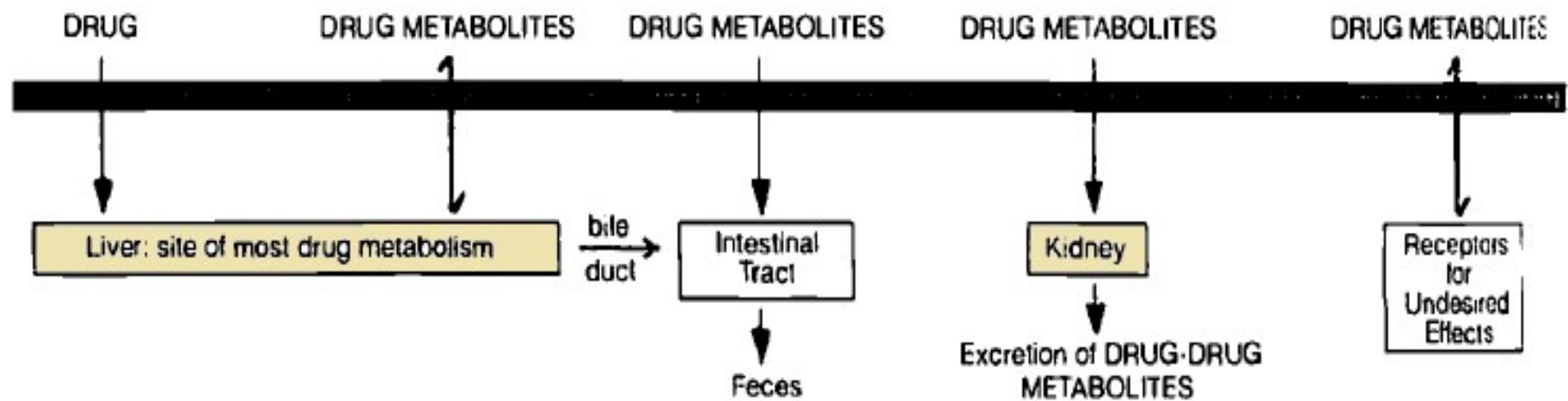
1. alkylating agents → cancer chemotherapy.
- 2.a few inhibitors of the enzyme Ach-I .
- 3.suicide inhibitors of MAO-I.

## Drug-administration:

1. orally
2. paranterally (I.V, I.M, S.C, )



DRUG ——— Serum Albumin **SYSTEMIC CIRCULATION**





Oral admin.:

-drug is either **solid** or **liquid**

as (solution) = absorb. through the GI mucosa.

The ability of the drug to dissolve is governed by several factors:

a- chemical structure

b- particle size and particle S.A.

c- nature of the crystal form

d- type of tablet coating, and type of tablet matrix.

\* varying the dosage form and physical characteristics  
possible to have a drug dissolve  
quickly or slowly

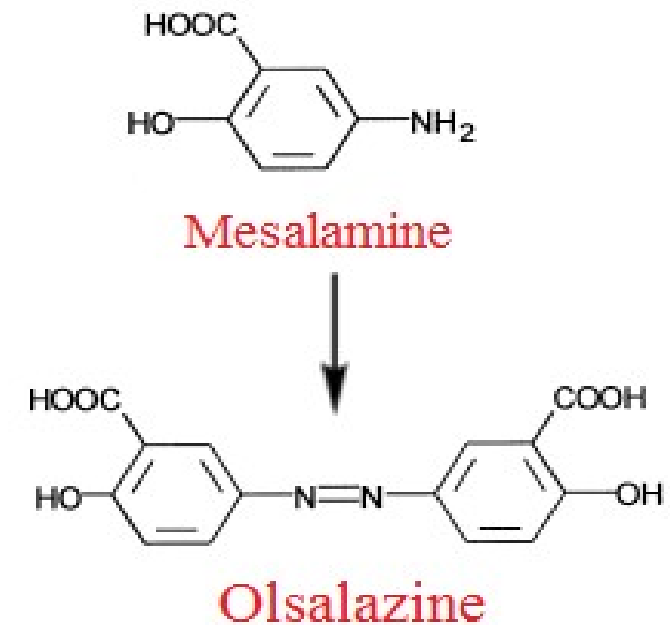
sodium phenytoin = ttt of epilepsy

variation of both the crystal form and tablet adjuvants  
can significantly alter the bioavailability of this drug

\* Chemical modification is also used to a limited extent to facilitate a drug reaching its desired target

Ex:

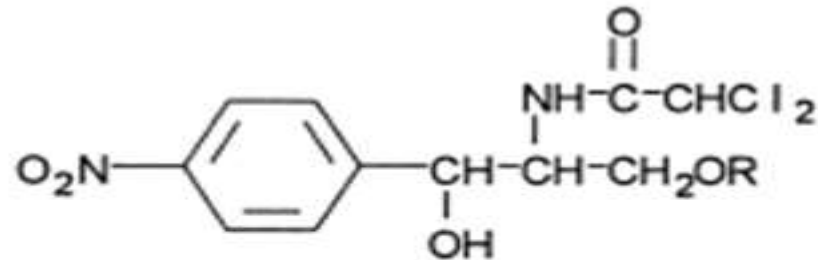
Olsalazine( NSAIDs) → ttt of ulcerative colitis.



\* dimer of the pharmacologically active **mesalamine** (5-aminosalicylic acid).

Other ex.

chloramphenicol antibiotic, has unpleasant taste  
chloramphenicol palmitate (*prodrugs*).

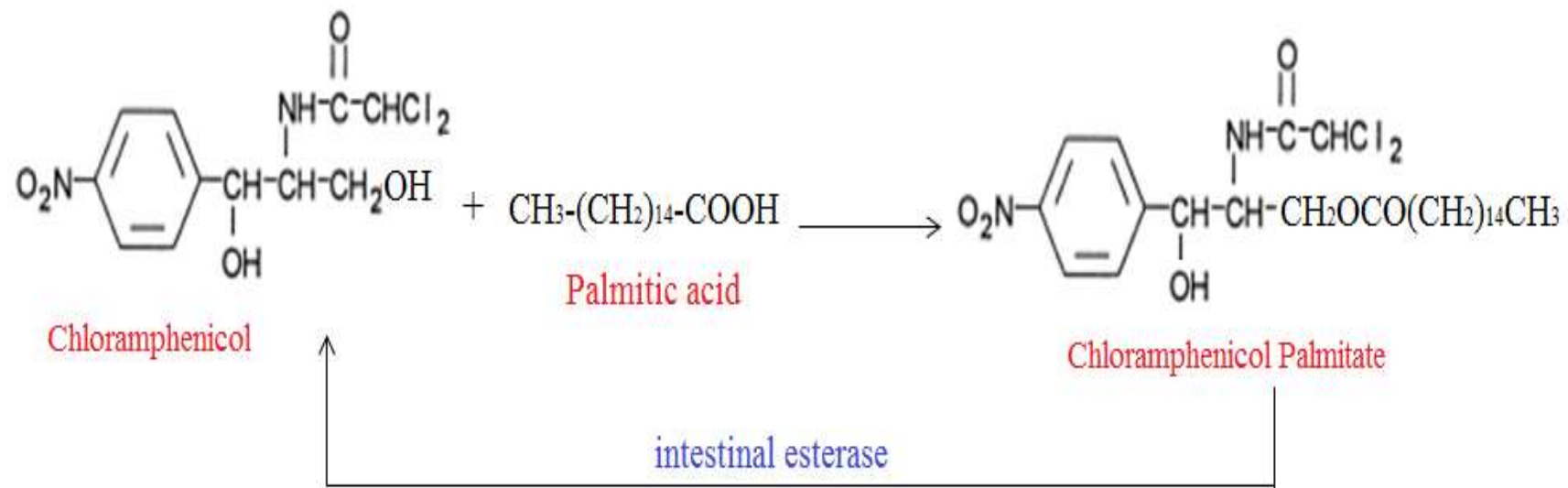


Chloramphenicol R= H

Chloramphenicol Palmitate R= CO(CH<sub>2</sub>)<sub>14</sub>CH<sub>3</sub>

\* In intestinal tract, the ester is hydrolyzed by the digestive esterase to the active chloramphenicol.

\* Prodrug???



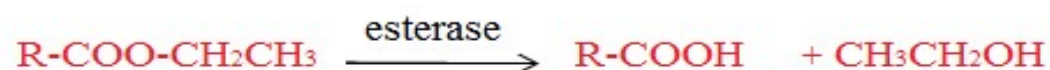
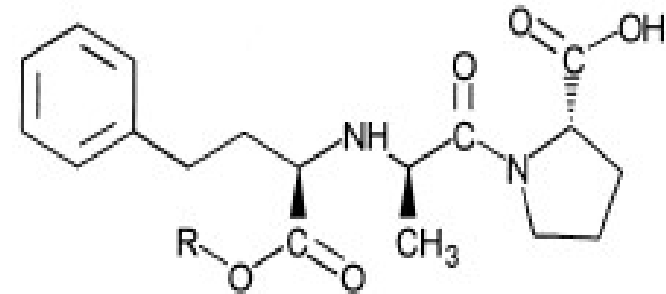
**Olsalazine and chloramphenicol palmitate** are examples of prodrugs. Most prodrugs are compounds that are inactive in their native form but are easily metabolized to the active agent.



\* Some time , **prodrug** approach is used to **enhance** the absorption of a drug from GIT .

Ex:

Enalapril = (ACE-I) .



Enalapril  
(inactive)

Enalaprilic acid

Enalapril: R = C<sub>2</sub>H<sub>5</sub>

Enalaprilic Acid: R = H

Much more readily  
absorbed orally

poorly abs. orally active  
pharmacologically active

\*Unless the drug is intended to act locally in the GIT , it will to pass through the GI mucosal barrier into venous circulation → receptor.

The drug's route involves distribution or partitioning between the aqueous environment of GIT , the lipid bilayer cell membrane of the mucosal cells, possibly the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the GIT , and the aqueous environment of venous circulation.

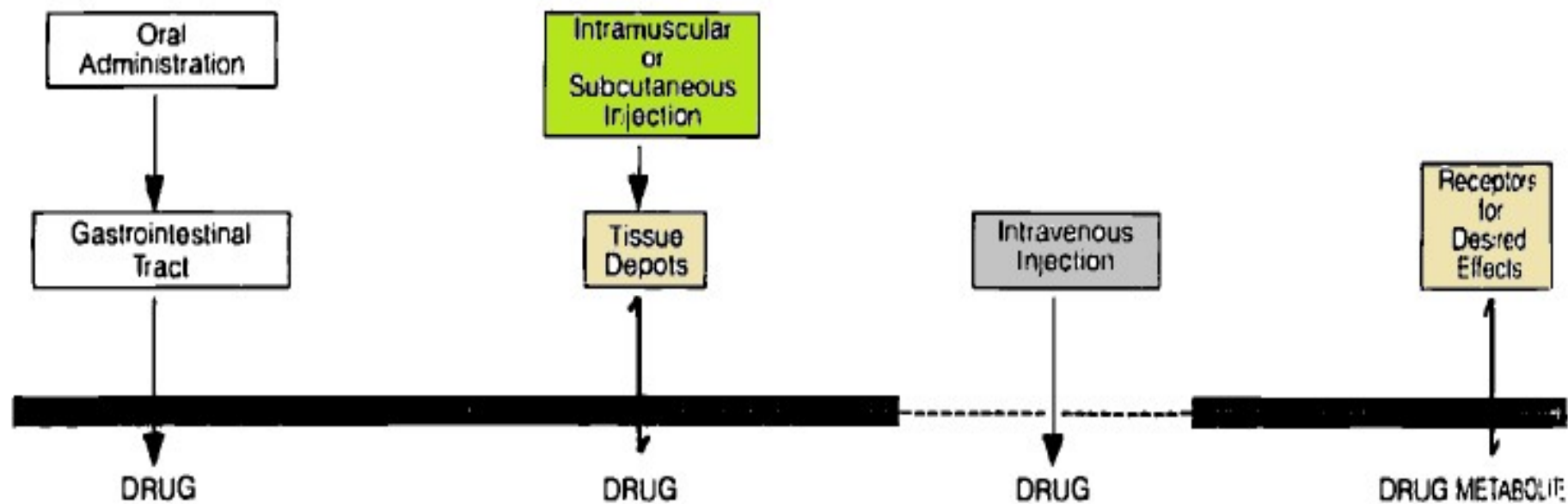
## Parenteral administration

This is common in **patients** who:

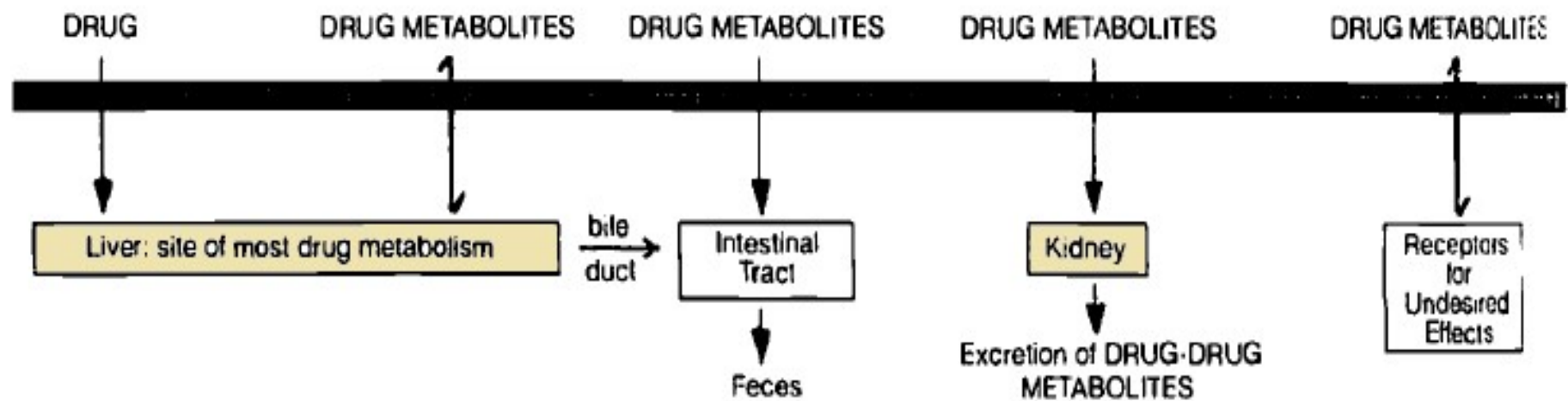
1. because of illness

2. cannot tolerate or are incapable of accepting drugs orally.

3. Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) .



DRUG ——— Serum Albumin **SYSTEMIC CIRCULATION**



## Parantral includes :

1) I.V adm. places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body, including :

a- tissue depots

b- the liver (most biotransformations)

c- the receptors.

2) Subcutaneous (S.C) and I.M. injections  
slow distribution of the drug, because it must diffuse  
from the site of injection into systemic circulation.

4) Intraspinal (I.S) and intracerebral (I.C) routes will place the drug directly into the spinal fluid or brain, respectively. It is possible to inject the drug directly into specific organs or areas of the body.

The prodrugs approach can be used to alter the solubility characteristic, can increase the flexibility in formulation (dosage forms)

e.g. **methyl prednisolone**

essentially water-insoluble

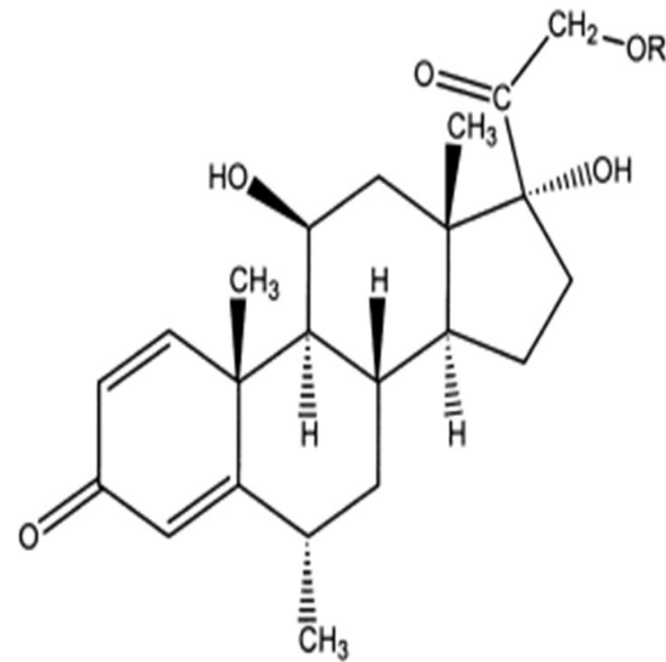
methylprednisolone acetate to

slightly water-insoluble

methylprednisolone

to water-soluble methylprednisolone

sodium succinate



Methylprednisolone: R = H

Methylprednisolone Acetate: R = C(=O)CH<sub>3</sub>

Methylprednisolone Sodium Succinate: R = C(=O)CH<sub>2</sub>CH<sub>2</sub>COO<sup>-</sup> Na<sup>+</sup>



## Protein Binding

Once the drug enters the systemic circulation , can undergo several events.

It may stay in solution, but many drugs will be bound to the serum protein:



Depending on  $K_{eq}$

## Protein binding can have a profound effect on:

1. solubility of drug.
2. Biodistribution[ e.g. Dr-alb. Complex can not passage through the placenta from maternal to fetal circulation]

### 3. Half-life in the body

- . the complex is too large to pass through renal glomerular membrane → preventing rapid excretion of the drug.

- . limit the amount available to biotransformation

- . limit the amount for interaction with Rec.

albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.)

4. **drug–drug interactions** that result when one drug displaces another from the binding site on albumin.

E.g. **anticoagulant warfarin-** albumin-binding sites.

This increases the effective concentration of **warfarin** at the receptor, leading to an **↑ed prothrombin** time and potential hemorrhage.

\* warfarin—alb. Complex + Dr. → Dr.—alb. Complex  
+ ↑ warfarin

hemorrhage → ↑ toxicity of warfarin