# تفريغ بيوفارما

**اسم الموضوع:**
Bioavailability (2)

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# Physicochemical and Formulation Factors For Improving Bioavailability

# Improving the bioavailability of drugs due to poor aqueous solubility

**Salts:** Formation of drug salts can significantly enhance drug solubility and dissolution, since the ionized form of the drug has much higher solubility

E.g. Diclofenac sodium, Amitriptyline Hydrochloride

# Improving the bioavailability of drugs due to poor aqueous solubility

**Amorphous solids** Drugs may exist in amorphous forms (e.g. cefuroxime axetil and quinapril hydrochloride), which have higher apparent solubility and faster dissolution compared to their crystalline counterparts.

# Improving the bioavailability of drugs due to poor aqueous solubility

## Amorphous solid dispersions

In amorphous solid dispersions, the drug is dispersed in its amorphous form in an inert carrier, which is commonly a polymer or a mixture of surfactant and polymer

لا يتفاعل مع الدواء

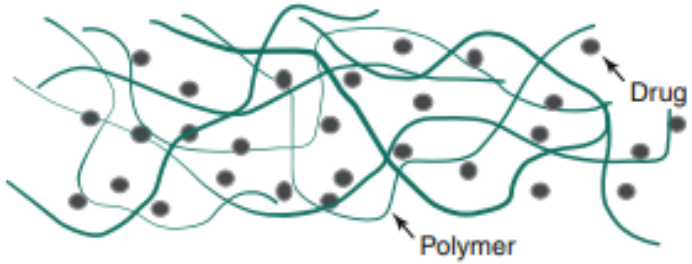



Fig. 20.7 Drug/polymer amorphous solid dispersion.

# Formulation approaches to improving drug bioavailability

**Cosolvents**

- Predissolving drugs in low molecular weight cosolvents (e.g. polyethylene glycols (PEGs), propylene glycol,glycerol) followed by filling the cosolvent solution into soft capsules;
- This approach has been utilized in several commercial formulations, with PEG 400 most commonly used

# Formulation approaches to improving drug bioavailability

**Cyclodextrin complexation**

- Cyclodextrins (CDs) are natural cyclical oligosaccharides produced by enzymatic modification of starch. by bacteria
- They are composed of glucopyranose units which form a ring of six (α-CD), seven (β-CD) or eight (γ-CD) units.

# Formulation approaches to improving drug bioavailability

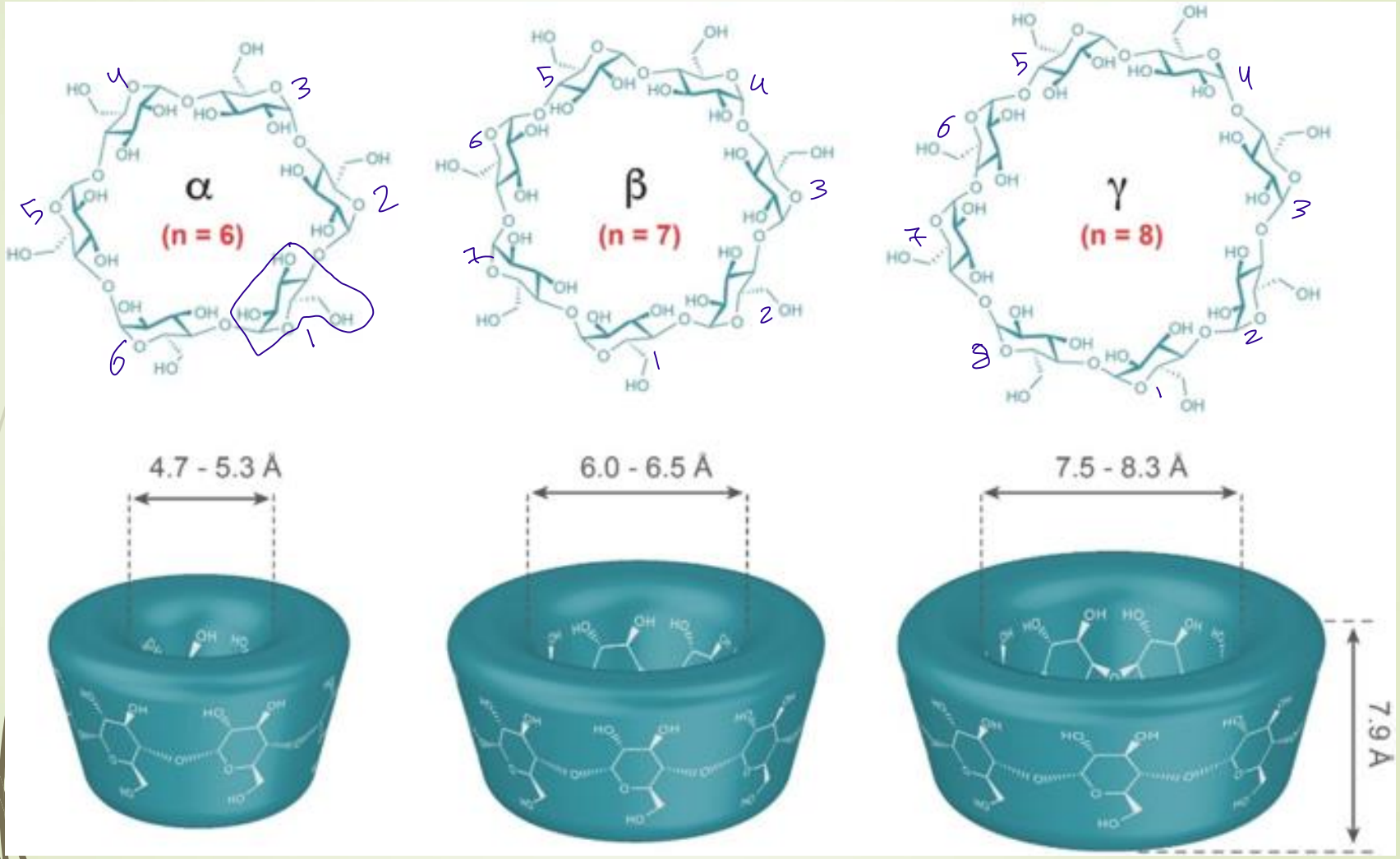
* اذا كانت الدواء Lipophilic يحفجوا

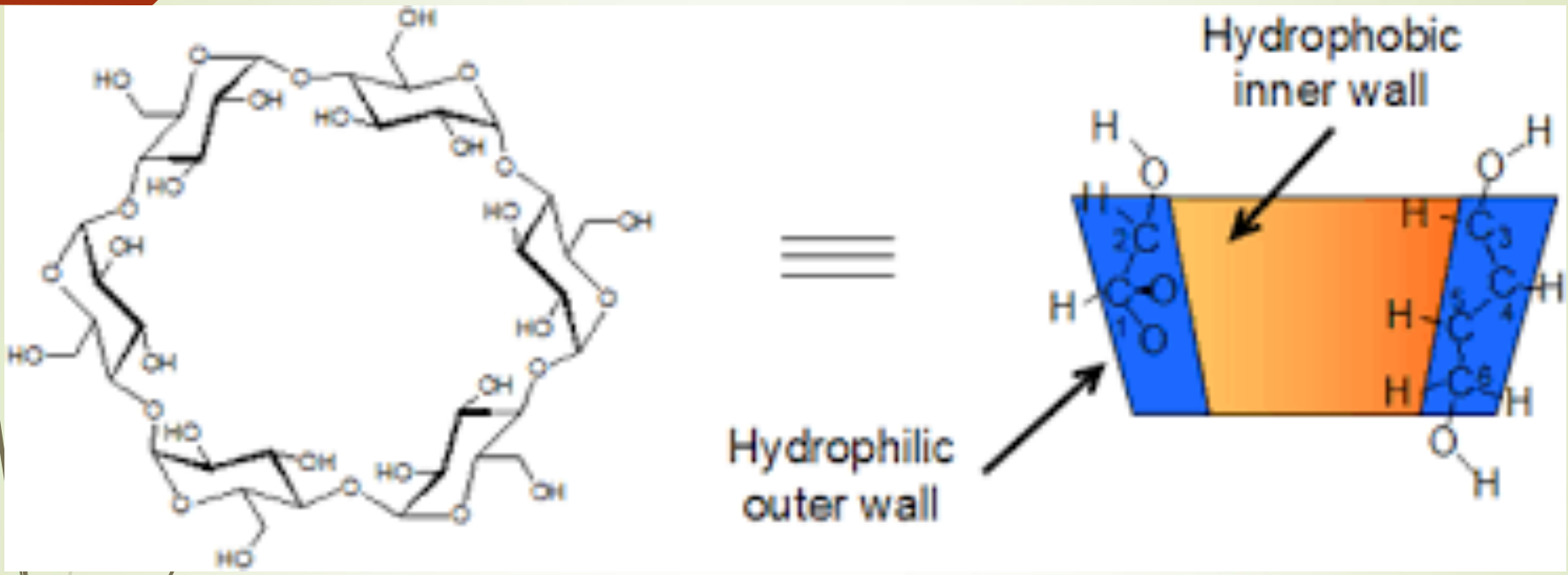
* منبرا hydrophobic

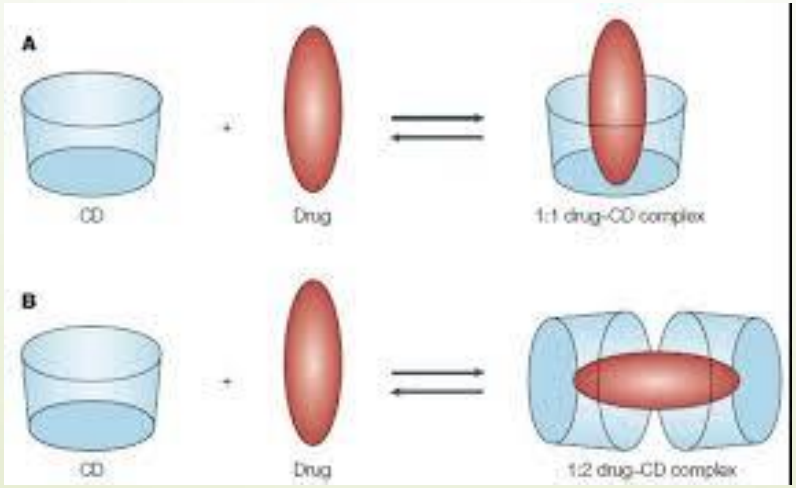
* منجوا Lipophilic

## Cyclodextrin complexation

- The outer surface of the ring is hydrophilic and the inner cavity is hydrophobic; they are often described as 'bucket-like' structures.
- Lipophilic molecules can fit into the cavity to form soluble inclusion complexes in aqueous solution.


α
(n = 6)
β
(n = 7)
γ
(n = 8)
4.7 - 5.3 Å
6.0 - 6.5 Å
7.5 - 8.3 Å
7.9 Å

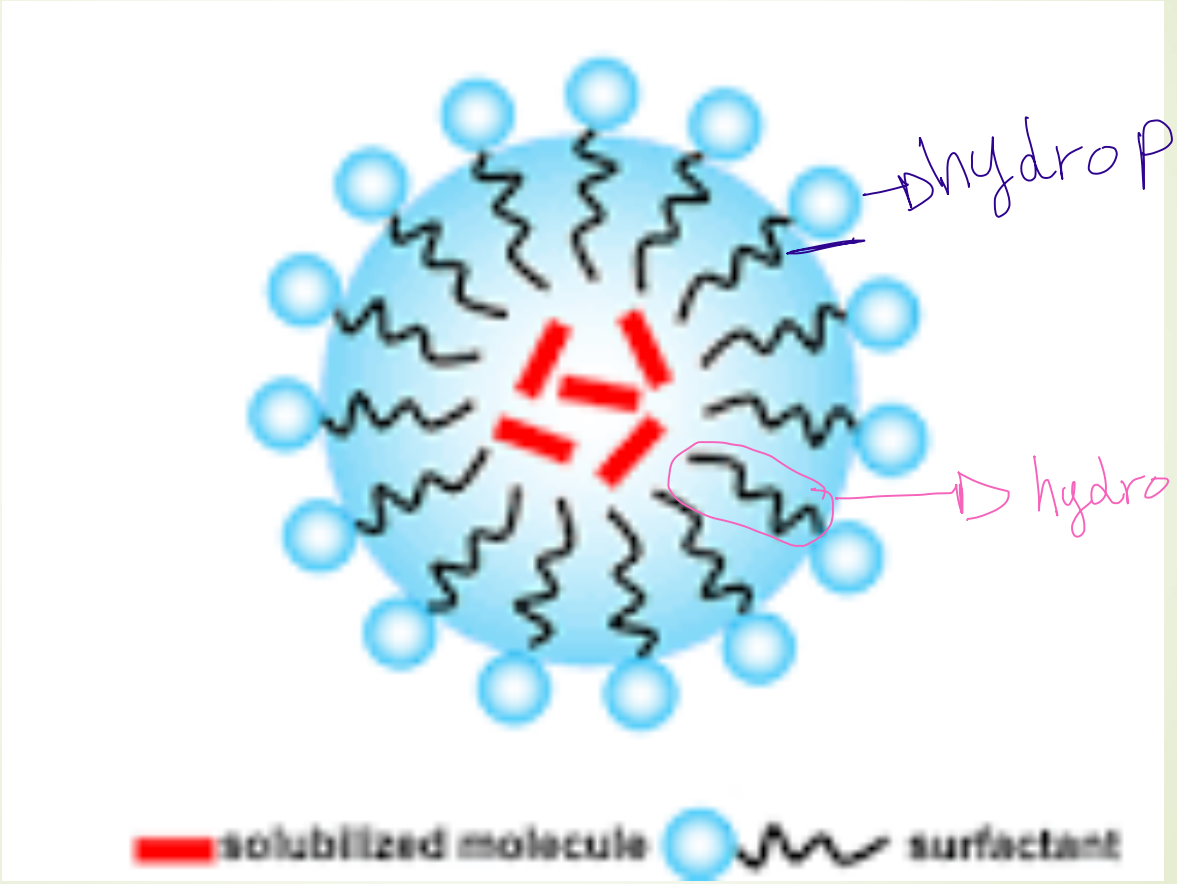

Hydrophobic
inner wall
Hydrophilic
outer wall


A
CD
Drug
1:1 drug-CD complex
B
CD
Drug
1:2 drug-CD complex

# Formulation approaches to improving drug bioavailability

**Micellar solubilization**

- The drug solubilization by surfactant micelles is a commonly used approach in aqueous liquid preparations to improve bioavailability.
- Surfactants may also be included for the same purpose in solid oral dosage forms.


hydrophilic
hydrophobic
solubilized molecule
surfactant

# Formulation approaches to improving drug bioavailability

**Self-emulsifying drug delivery systems**

- In self-emulsifying drug delivery systems, drug is solubilized in an oil/surfactant vehicle and filled into a soft capsule.
- On contact with gastrointestinal fluids, the contents form a microemulsion or nanoemulsion spontaneously.

# Formulation approaches to improving drug bioavailability

**Self-emulsifying drug delivery systems**

- The emulsion droplets formed maintain drug in solution for a prolonged period even after dilution in gastrointestinal fluids.
- The small droplets have a high surface area facilitating rapid diffusion of drug from the dispersed oil phase into the aqueous intestinal fluids, enhancing drug absorption.

# Improving the bioavailability of drugs with poor permeability

**Permeation enhancers**

- The rate-limiting step for the absorption of BCS class III drugs is permeability, which can potentially be improved by using permeation enhancers.
- Permeation enhancers work to increase drug permeability mainly through
  - (i) the paracellular route by reversibly opening the tight junctions and/or
  - (ii) the transcellular route by altering membrane integrity through disruption of the lipid bilayer

# Improving the bioavailability of drugs with poor permeability

## Permeation enhancers

- Numerous permeation enhancers are being investigated in clinical trials; these include:

1. surfactants,
2. bile salts,
3. medium chain fatty acids
   - Fatty acids and bile salts are mild surfactants that act by fluidizing the gastrointestinal membrane.
4. chelating agents (e.g. ethylenediamine tetraaceticacid; EDTA).
   - EDTA chelates calcium, thereby altering the tight junctions.

# Improving the bioavailability of drugs with poor permeability

**Permeation enhancers**

- They offer particular promise in the oral delivery of peptides and proteins.
- Semaglutide is a polypeptide indicated for adults with type 2 diabetes, which became available as a once-daily tablet formulation at the end of 2019 (**Rybelsus**).
- This product utilizes a small fatty acid derivative, sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC), as a permeation enhancer.

# Biopharmaceutical classification system (BCS)

The BCS categorizes drugs into four types depending on their solubility and permeability characteristics:

- Class I: High solubility—High permeability
- Class II: Low solubility—High permeability
- Class III: High solubility—Low permeability
- Class IV: Low solubility—Low permeability

# Assessment of biopharmaceutical properties

# Assessment of biopharmaceutical properties

Biopharmaceutics is concerned with the factors that influence the rate and extent of drug absorption, which include the factors that affect:

1. the release of a drug from dosage form and its dissolution in physiological fluids
2. its stability within those fluids
3. its ability to cross the relevant biological membranes
4. its presystemic metabolism

# Assessment of Release of a drug from its dosage form into solution

- The solubility of a drug across the gastrointestinal pH range will be one of the first indicators as to whether dissolution is liable to be rate limiting in the absorption process.
- The aim of dissolution testing is to measure an in vitro characteristic of a potential formulation that reflects its in vivo performance.
- Several pharmacopeial methods are used and their standards regarding apparatus design and operation are discussed in pharmacopeia which include:

# Assessment of Release of a drug from its dosage form into solution

## USP Apparatus 1: Basket


# Assessment of Release of a drug from its dosage form into solution

## USP Apparatus 2: Paddle

# Assessment of Release of a drug from its dosage form into solution

## USP Apparatus 4 (Flow-Through Cell)


Useful for low solubility drugs

# Assessment of Release of a drug from its dosage form into solution

When designing a dissolution test to assess drug release from a biopharmaceutical perspective, it is important to mimic as closely as possible the conditions of the gastrointestinal tract.

Clinical scientists increasingly want to rely on dissolution tests to establish **in vitro-in vivo correlations (IVIVCs)** between the release of the drug from the dosage form and its absorption.

# Assessment of Drug Stability in physiological fluids

The stability of drugs in physiological fluids (in the case of orally administered drugs, the gastrointestinal fluids) depends on two factors:

- the chemical stability of the drug across the gastrointestinal pH range, i.e. the drug's pH stability profile between pH 1 and pH 8; and
- its susceptibility to enzymatic breakdown by the gastrointestinal fluids.

# Assessment of Drug Stability in physiological fluids

- The stability of a drug in gastrointestinal fluids can be assessed by using simulated gastric and intestinal fluids or by obtaining gastrointestinal fluids from humans or animals.
- In general, the drug is incubated with either real or simulated fluid at 37 °C for 3 hours and the drug content is analysed. A loss of more than 5% of the drug indicates potential instability

# Assessment of Drug Permeability through biological membranes

A wealth of techniques is available for either estimating or measuring the rate of drug permeation across membranes. These include:

1. Computational/ in silico
2. Physicochemical
3. Cell culture
4. Excised tissues
5. In situ studies
6. In vivo studies

# Assessment of Drug Permeability through biological membranes

**Some models available for predicting or measuring drug absorption**

| Model type | Model | Description |
|---|---|---|
| Computational/ in silico | clog P | Commercial software that calculates the n-octanol/water partition coefficient based on fragment analysis, known as the Leo Hansch method |
| Physico-chemical | Partition coefficient | Measure of lipophilicity of a drug, usually measured between n-octanol and aqueous buffer via a shake-flask method |
| Cell culture | Caco-2 monolayer | Measures transport across monolayers of differentiated human colon adenocarcinoma cells |

# Assessment of Drug Permeability through biological membranes

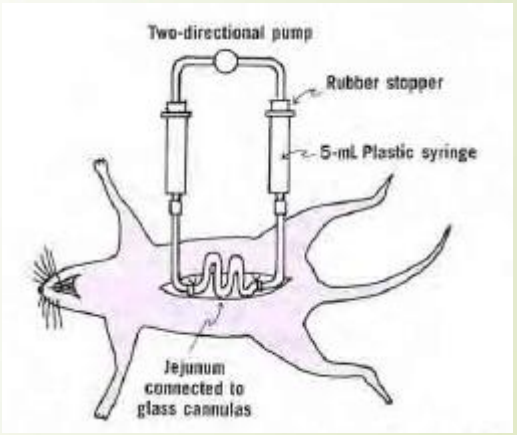
**Some models available for predicting or measuring drug absorption (continued)**

| Model type | Model | Description |
|---|---|---|
| Excised tissues | Cells | Measures uptake into cell suspensions, e.g. erythrocytes |
| | Everted sacs | Measures uptake into intestinal segments/sacs |
| | Isolated sheets | Measures the transport across sheets of intestine |
| Perfusion studies | Intestinal loop | Measures drug disappearance from perfusate of loop of intestine in animals |

# Assessment of Drug Permeability through biological membranes

Partition coefficient

Everted sac




In situ rat intestinal absorption

# Assessment of Drug Permeability through biological membranes

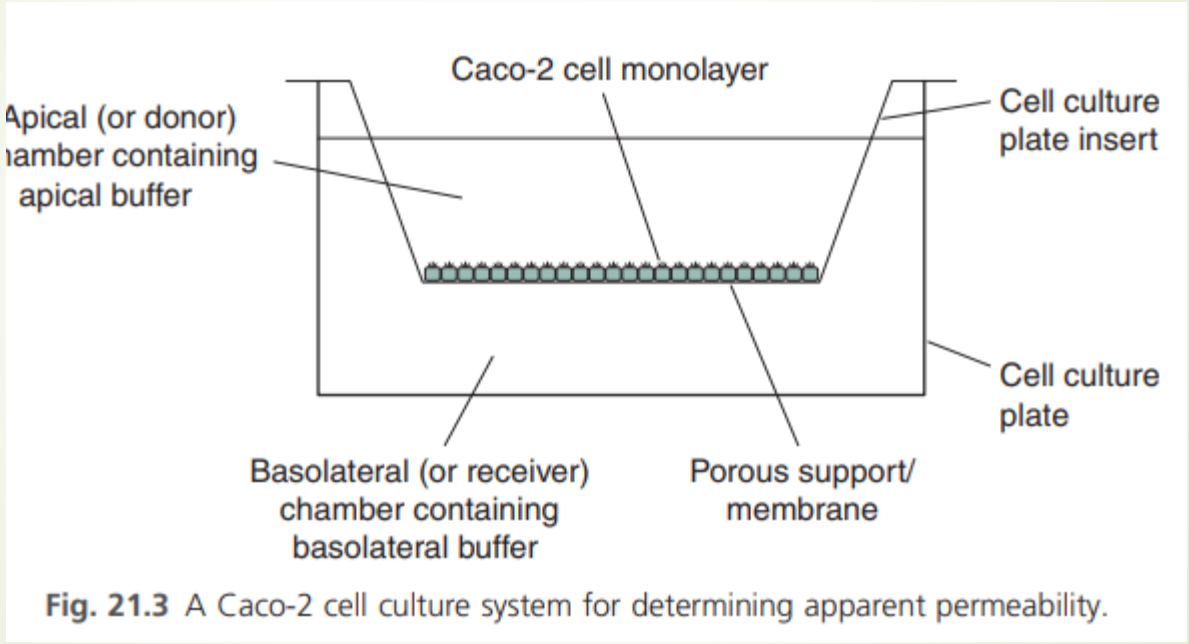



**Fig. 21.3** A Caco-2 cell culture system for determining apparent permeability.

# Assessment of Presystemic metabolism

- Presystemic metabolism occurs before a drug reaches systemic circulation, primarily in the gut wall and liver for orally administered drugs.
- Intestinal presystemic metabolism can be studied using gut wall homogenates, where drugs are incubated and analyzed for metabolic changes.
- Various liver preparations, including microsomes, isolated hepatocytes, and liver slices, are used to study hepatic metabolism