आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

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E-Content

IFTM University, Moradabad

Absorption of drugs

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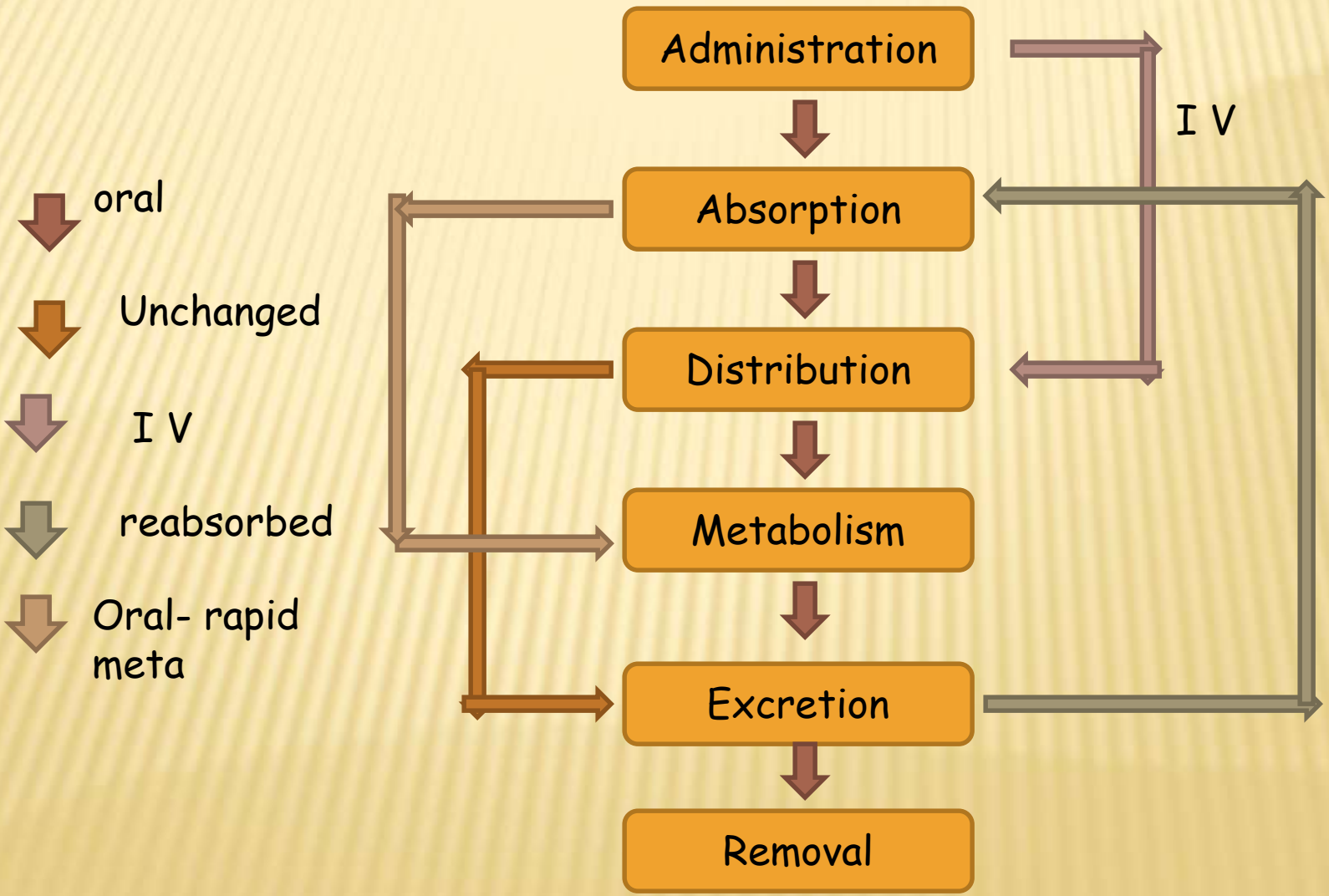
Overview

- Definition
- Mechanism of drug absorption
- Factors affecting drug absorption & bioavailability

Pharmacokinetics Process

Pharmacokinetics Process



Definition

- Movement of unchanged drug from site of administration to systemic circulation

Absorption /bioavailability from common routes of drug administration

Enteral

- Buccal / sublingual
- Oral
- Rectal

Parenteral

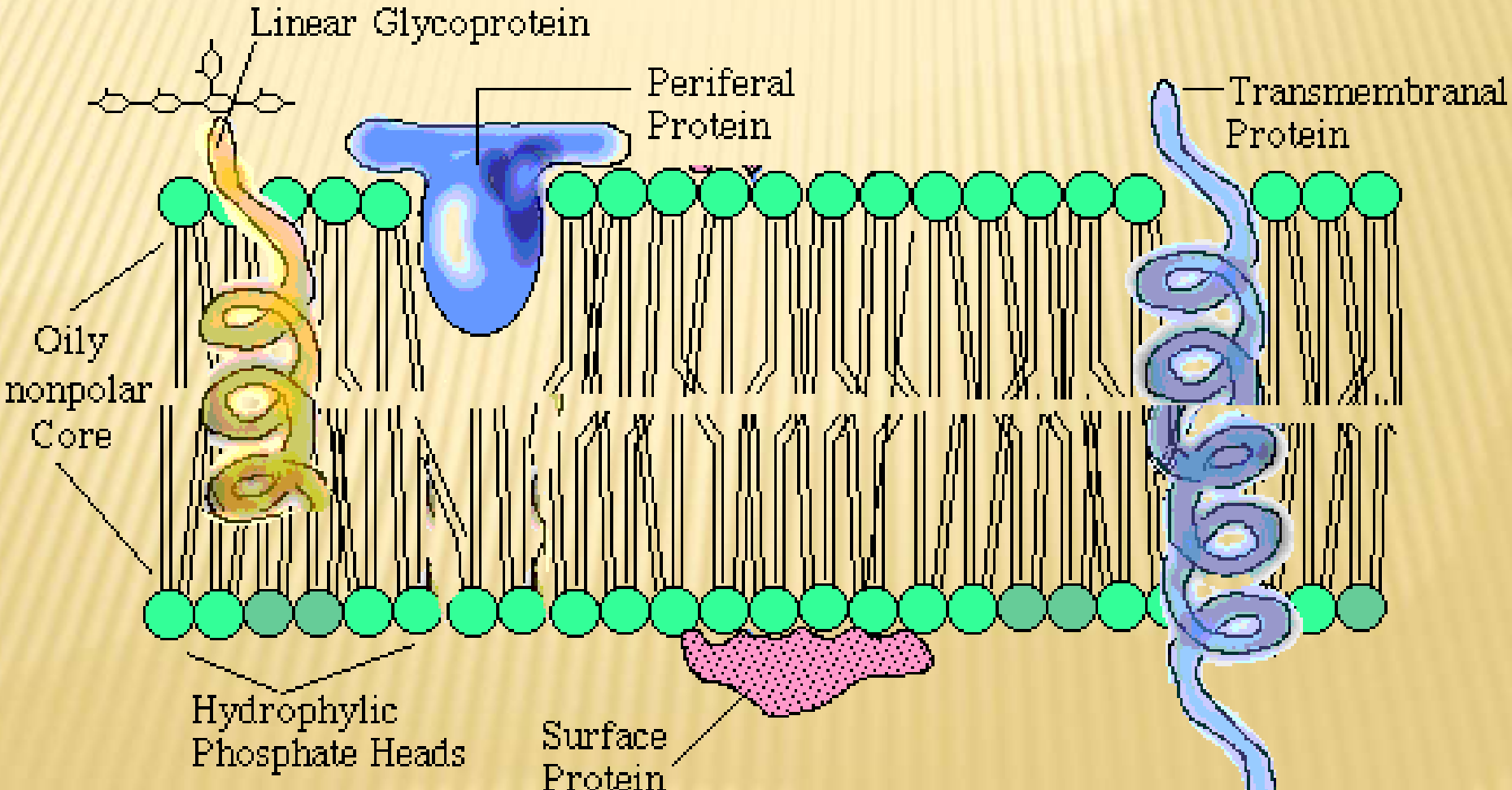
- Intravenous
- Intramuscular
- Subcutaneous
- Inhalation

Topical

- Transdermal
- Mucous membrane
- Ocular

Absorption from GIT

- Cell membrane : structure and physiology



Mechanism of drug absorption

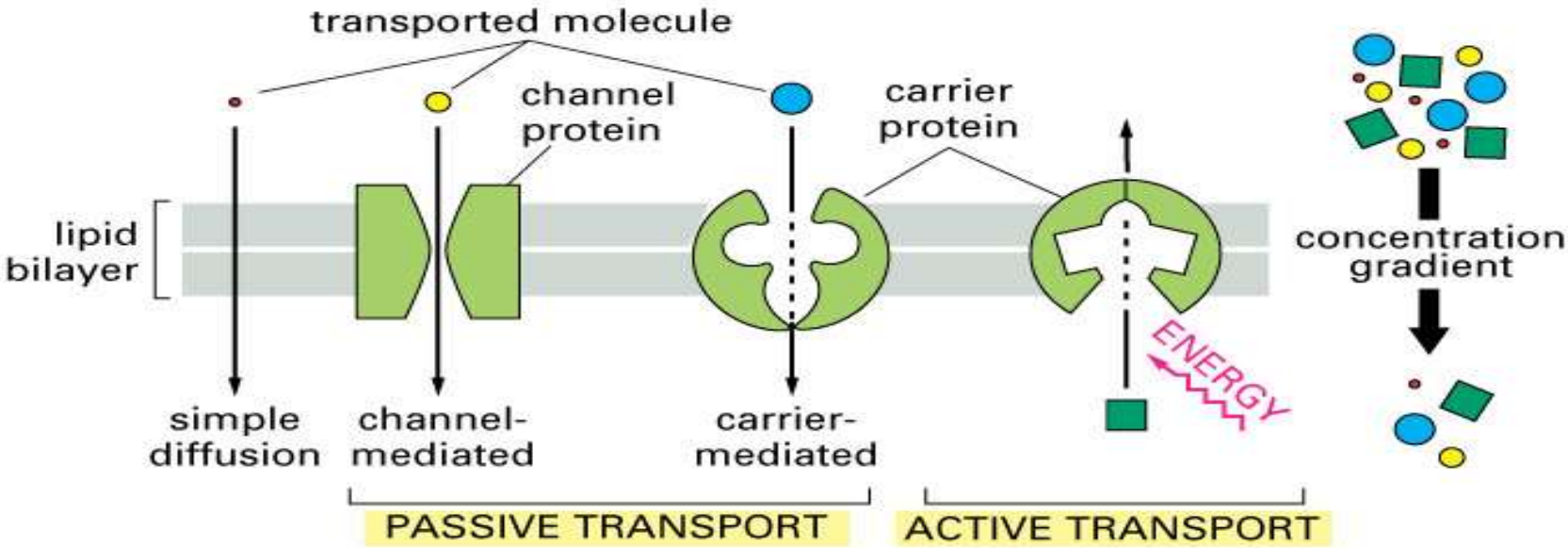


Figure 12-4 Essential Cell Biology, 2/e. (© 2004 Garland Science)

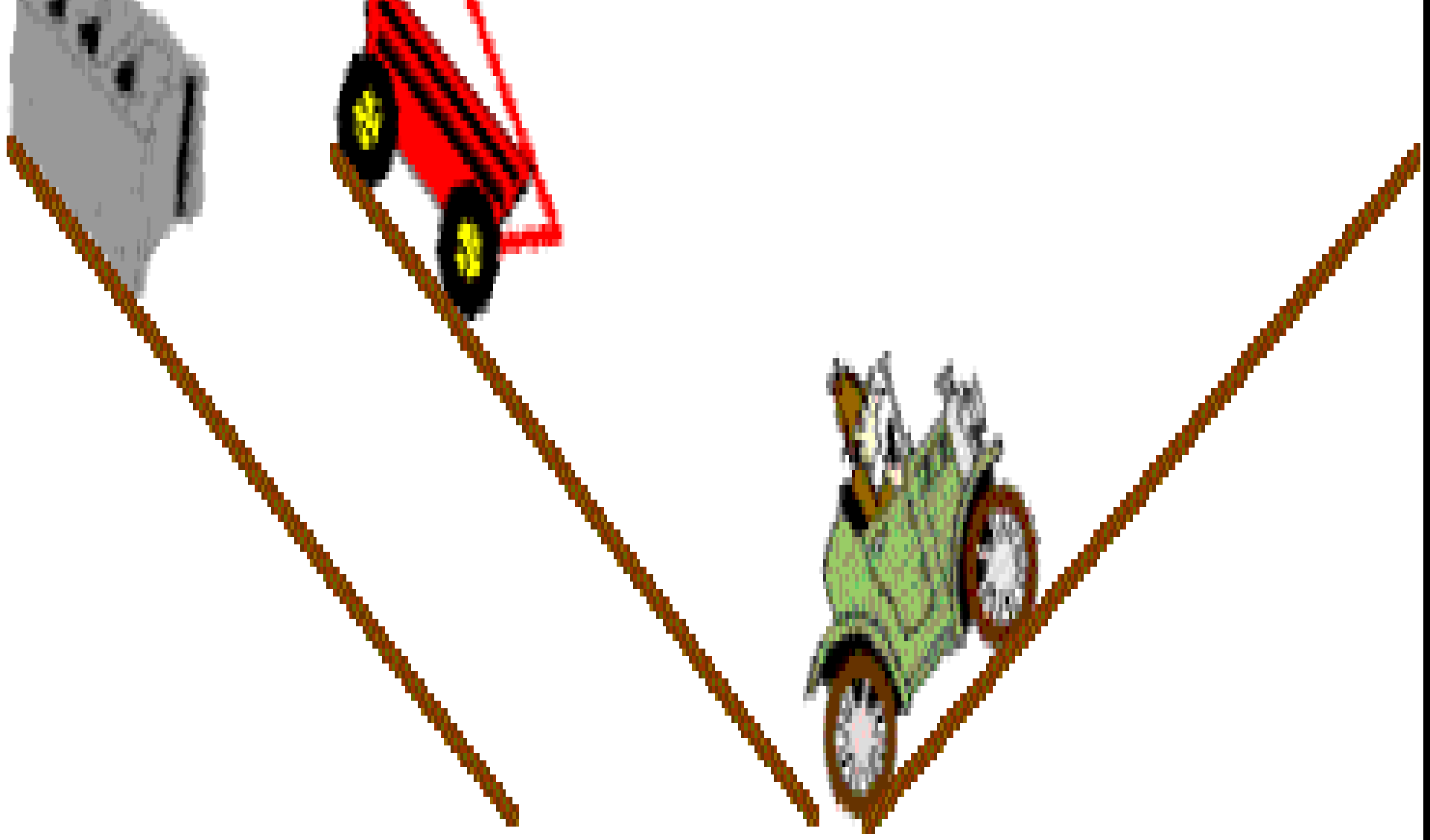
- Transcellular / Intracellular transport
  Passage across GI epithelium

1. Passive transport process
2. Active transport process

- Paracellular / Intercellular transport
  Transport through junctions between GI epithelium

- Vesicular / Corpuscular transport
  Transport of substances within vesicles into cells

1. Pinocytosis
2. Phagocytosis


Passive
Facilitated
Active

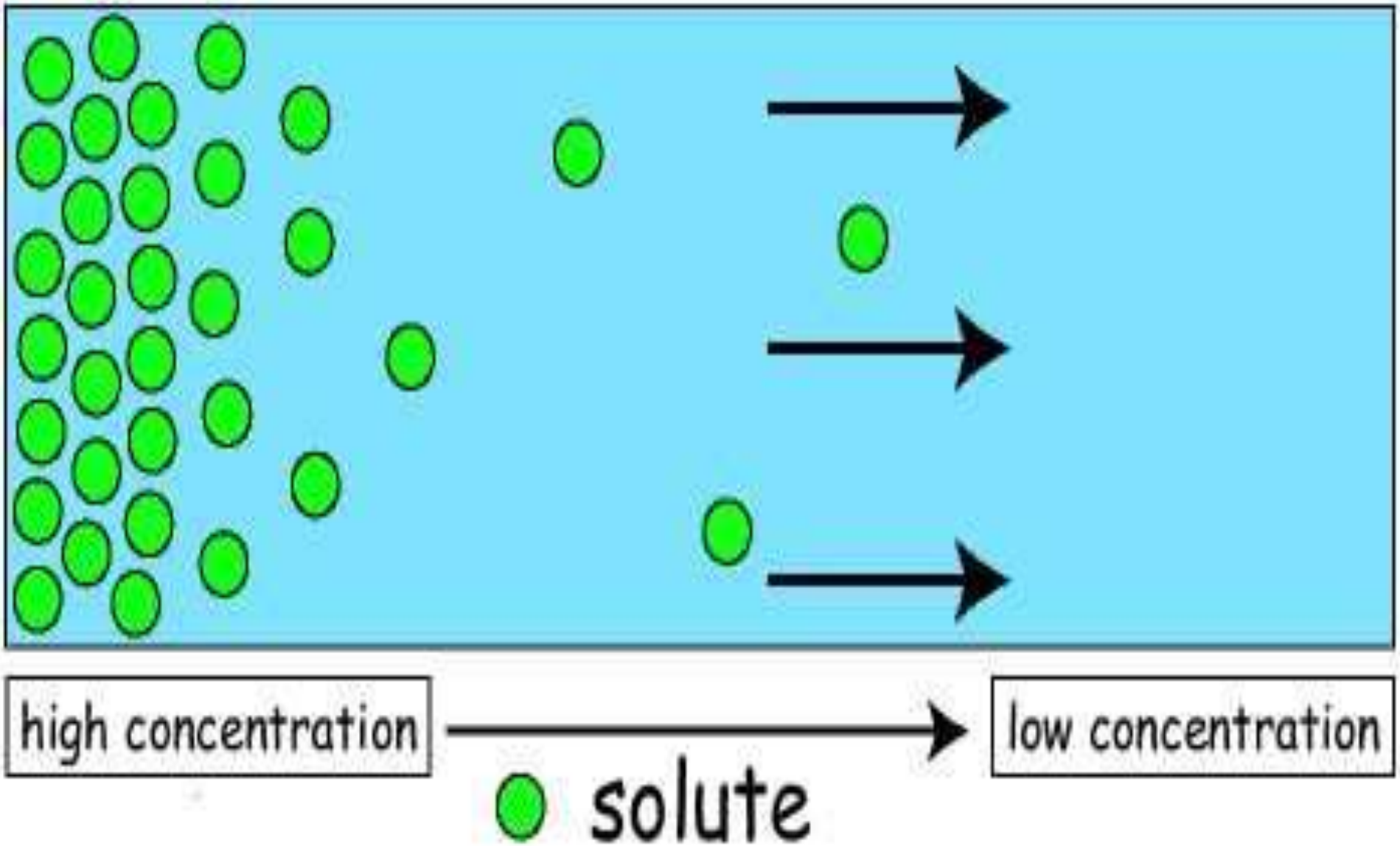
Passive diffusion

- Non – Ionic diffusion
- Major process for absorption of 90% of drugs
- Driving force- Concentration or electrochemical gradient
- It follows Fick's first law of diffusion

Drug molecules diffuse from region of higher concentration to one lower concentration until equilibrium is attained and that the rate of diffusion is directly proportional to concentration gradient across membrane

$$dQ/dT=k\,[Cgit - C\,]$$

Diffusion



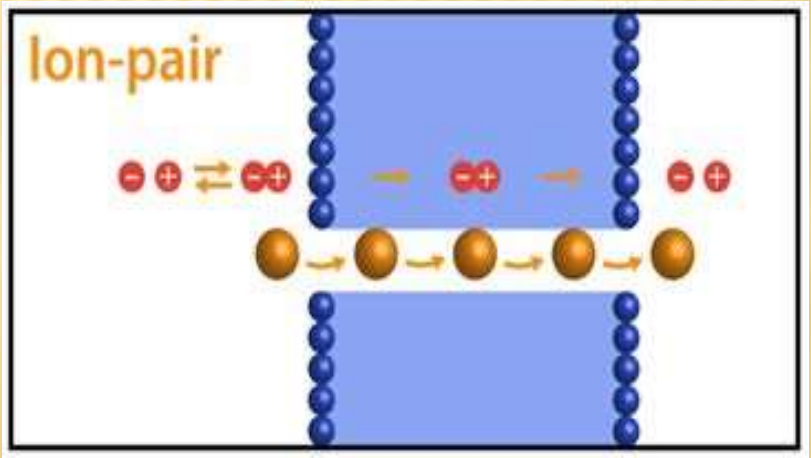
Pore transport

- Convective transport , bulk flow or filtration
- Responsible for transport of molecules into cells
- Driving force- hydrostatic force or osmotic differences across membrane
- Important in absorption of low molecular weight {<100}, low molecular size , chain like linear compounds molecular weight up to 400 daltons

Ion-pair transport

- Penetration of membrane by forming reversible neutral complexes with endogenous ions of GIT (mucin)

- Example propranolol with oleic acid

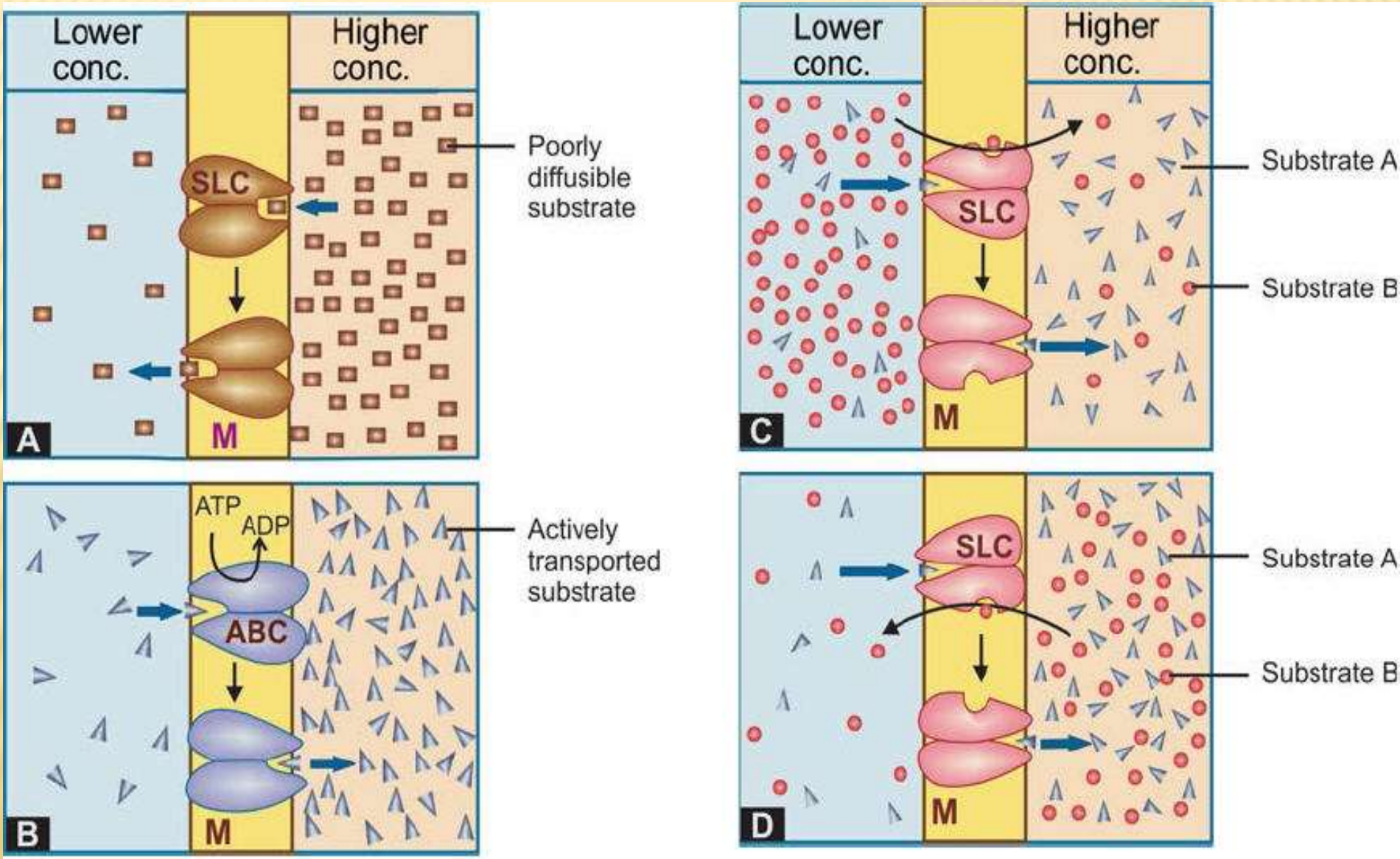


Carrier mediated transport

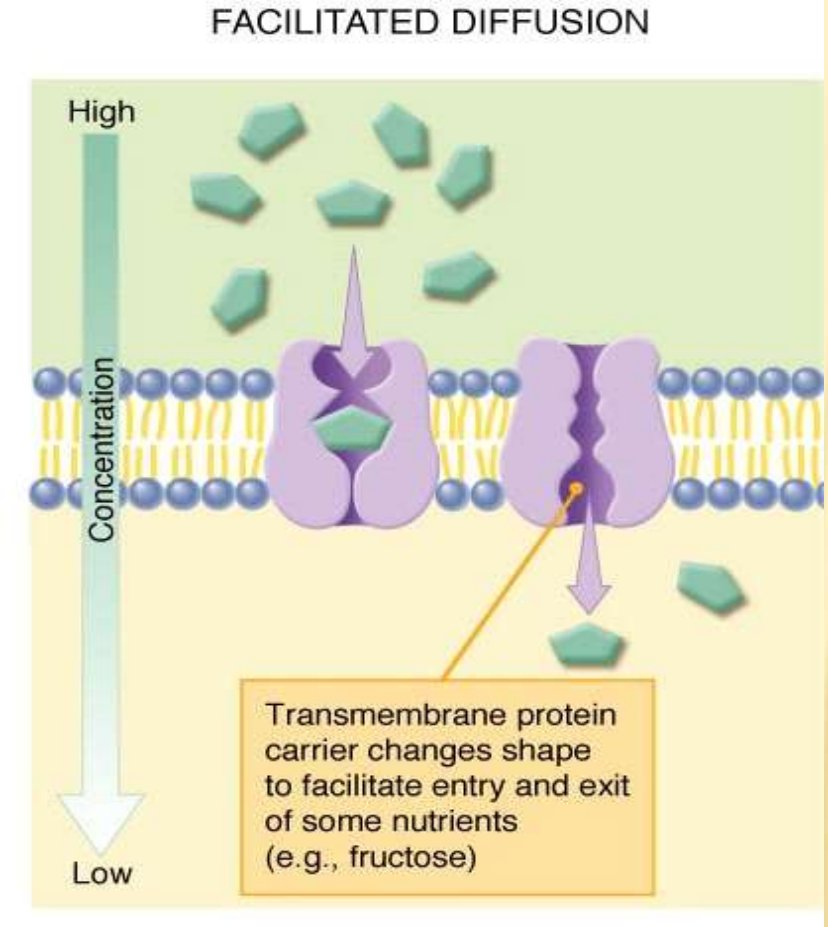
- Carrier (component of membrane) binds reversibly or non covalently with solute molecules and complex traverses to other side of membrane

1. Carriers – Unidirectional
2. Structure specific
3. Capacity limited

Specialized transport- carrier transport



Facilitated diffusion



- Carrier mediated transport operates down the concentration gradient (downhill transport)
- Driving force – Concentration gradient
- No energy expenditure
- Example vitamin B12

Active transport

- Requires energy in the form of ATP

  Primary active transport

  Requires direct energy

  Types

1} Ion transporters

  Transporting ion in or outside the cell

  Example ATP driven ion pump is proton pump

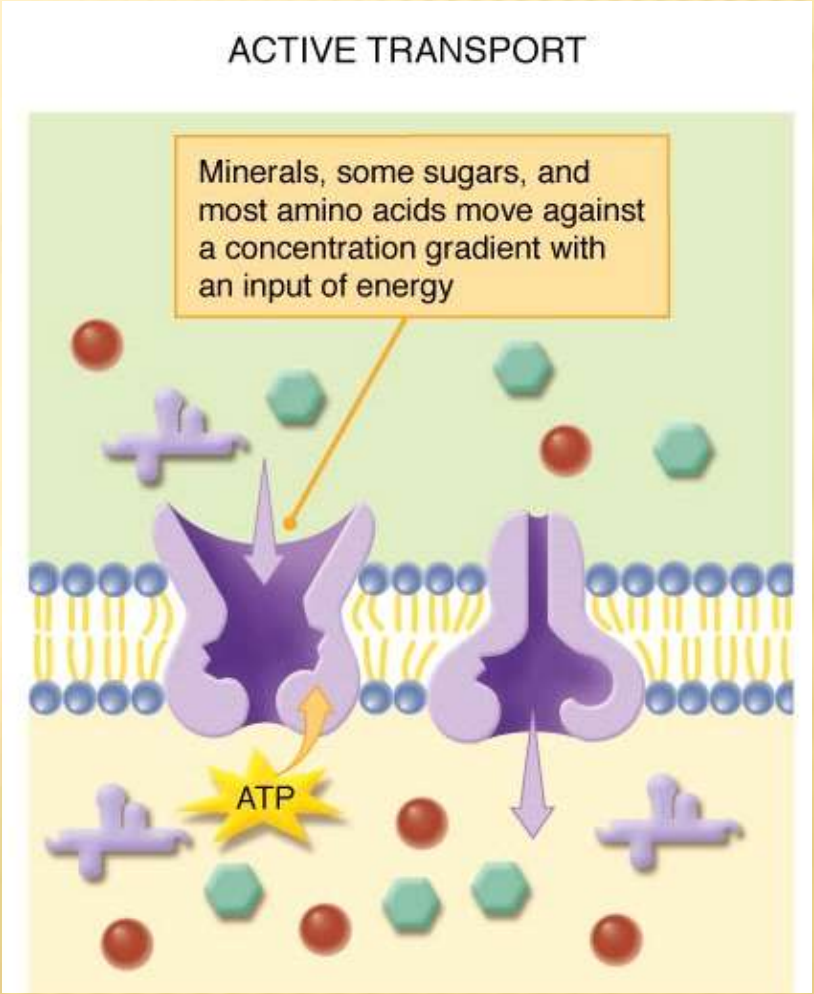
2} ABC [ATP binding cassette] transporters

  Responsible for transporting small foreign molecules out of the cells (exsorption)

Example

  P – glycoprotien multidrug resistance protein

  ABC transporters in brain capillaries



Secondary active transport

No direct energy requirement

1] Symport (co – transport)

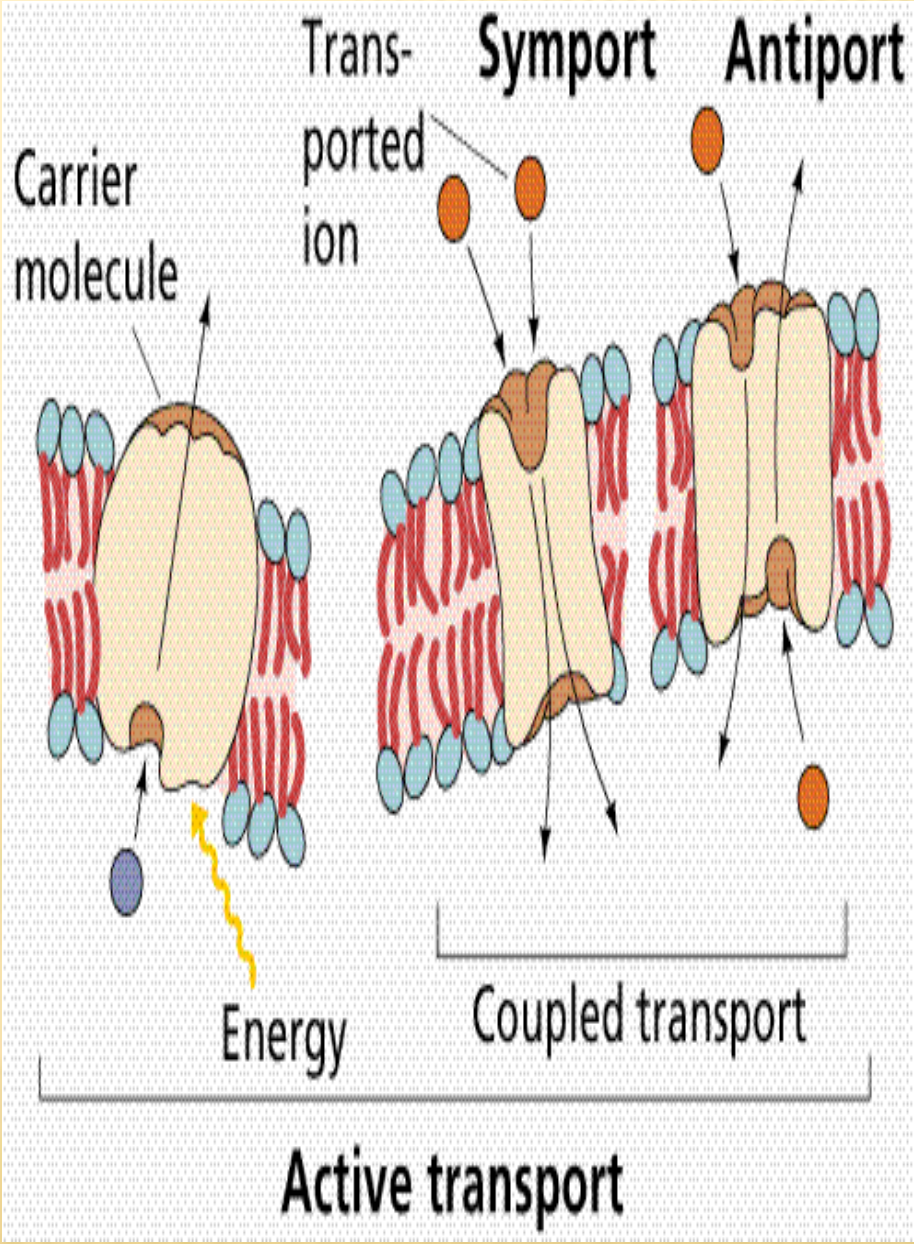
Transport of both molecules in same direction

Example H+ coupled peptide transporter (PEPT1) implicated in intestinal transport of beta lactam antibiotics

2] Antiport (counter – transport)

Movement of molecules in opposite direction

Example expulsion H+ using Na+ gradient in kidneys



Endocytosis

Minor transport mechanism involving engulfing extracellular materials within segment of cell membrane to form a saccule or vesicle then pinched of intracellularly

Drug or compound not required to be aqueous solution to get absorbed

Example cellular uptake of macromolecular nutrients like fats ,starch, oil soluble vitamins A,D,E and K

1] Phagocytosis (cell eating)

2] Pinocytosis (cell drinking)

Combined absorption mechanism

Example

- Cardiac glycosides

Absorbed by both passive & active transport

- Vitamin b12

Absorbed by passive diffusion, facilitated diffusion as well as endocytosis

Phases of drug transfer from GI absorption site(GI epithelium)into systemic circulation

- Preuptake phase
  - Dissolution of drug in GI fluids
  - Metabolism of drug in GI lumen
- Uptake phase
  - Delivery to absorption site in GIT
  - Metabolism in GI epithelium
  - Passage through GI epithelium
- Post-uptake phase
  - Metabolism in liver
  - Enterohepatic circulation of drug
  - Transfer into systemic circulation

Factors influencing drug absorption and bioavailabilty

Pharmaceutical factors

Physicochemical properties

1. Drug solubility and dissolution rate
2. Particle size and effective surface area
3. Polymorphism and amorphism
4. Pseudopolymorphism
5. Salt form of drug
6. Lipophilicity of drugs
7. pKa of drug and GI pH
8. Drug stability
9. Stereochemical nature

Dosage form and pharmaceutical ingredients

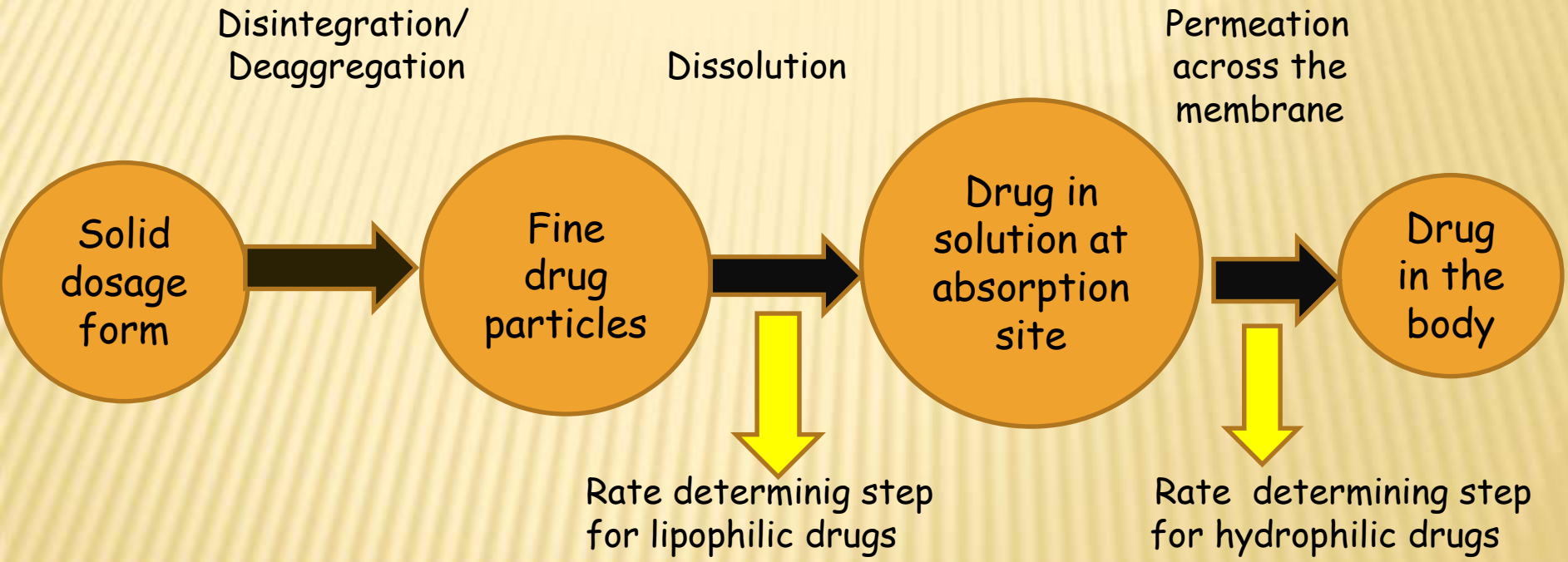
1. Disintegration time
2. Dissolution time
3. Manufacturing variables
4. Pharmaceutical ingredients
5. Nature and type of dosage form
6. Product age and storage conditions

Patient related factors

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal pH
5. Blood flow through GIT
6. Gastrointestinal contents
7. Presystemic metabolism
   - Luminal enzymes
   - Gut wall enzymes
   - Bacterial enzymes
   - Hepatic enzymes

Physicochemical factors

A] Drug solubility and dissolution rate



Dissolution rate : Amount of solid substance that goes into solution per unit time under standard conditions of temperature , pH and solvent composition and constant solid surface area

Class	Solubility	Permeability	Absorption pattern	Rate limiting step in absorption	Examples
1	High	High	Well absorbed	Gastric emptying	Diltiazem
2	Low	High	Variable	Dissolution	Nifedipine
3	High	Low	Variable	Permeability	Insulin
4	Low	Low	Poorly absorbed	Case to case	Paclitaxel

B] Particle size and effective surface area of drug

Surface area ↑ with ↓ particle size

Micronisation will result in higher dissolution rate

Example griseofulvin , chloramphenicol and several salts of tetracycline

D] Hydrates / Solvates (polymorphism)

Hydrate (drug in association with water)

Anhydrous (drug not in association with water) greater aqueous solubility

Example anhydrous theophylline and ampicillin higher aqueous solubility

E] Salt form of drug

Salts of weakly acidic drugs are highly water soluble

Example tolbutamide and phenytoin sodium have better bioavailability than there parent compounds

F] Drug pKa and lipophilicity

For drug compound molecular weight > 100 primarily transported by passive diffusion the process of absorption is governed by

1.Dissociation constant of drug pKa of drug

2.Lipid solubility of drug (function of Ko/wp)

3.pH at absorption site

The relation ship between P^H , pka and the extent of ionization is given by ***HANDERSON-HESSELBACH*** equation.

For weak acids

$$P^H = pka + \log(\text{ionized drug}/\text{un ionized drug})$$

For weak bases

$$P^H = pka + \log(\text{un ionized drug}/\text{ionized drug})$$

Acidic drugs are unionized at acidic P^H ,and absorption starts from stomach .

Very weak acids	**Unionized at all p^H values absorbed along the entire length of G.I.T.**	**Phenobarbital& Phenytion**
Moderately weak acids	Unionized at gastric P^H, ionized at intestinal P^H and better from stomach.	Cloxacillin,Aspirin , ibuprofen.
Stronger acids	Ionized at all P^H . Poorly absorbed from G.I.T	Di sodium cromoglycolate
Very week bases	Unionized at all p^H values absorbed along the entire length of G.I.T	Theophyllin, caffeine, diazepam
Moderately weak bases	ionized at gastric P^H, unionized at intestinal P^H and better from intestine.	Reserpine, codeine.
Stronger bases	Ionized at all P^H . Poorly absorbed from G.I.T	Guanethidine

- In stomach

Type of drug	Non-ionized Lipid soluble	Ionized Water soluble	Absorption
Weak acidic e.g. aspirin	More amt	Less amt	More
Weak basic	Less amt	More amt	Less

- In intestine

Type of drug	Non-ionized Lipid soluble	Ionized Water soluble	Absorption
Weak acidic	Less amt	More amt	Less
Weak basic e.g. chloroquine	More amt	Less amt	More

G] Drug stability

stability problems resulting in poor bioavailability

1. Degradation into inactive form
2. Drug interaction with one or more different components of dosage form or those present in GIT

H] Stereochemical nature

60% of drugs in current use are chiral

Optical isomers differ in potency of pharmacological effect

Dosage form (Pharmaco-technical) factors

A] Disintegration time

- Important for tablets and capsules
- Coated tablets: long Disintegration time
- Disintegration time is proportional to Amount of binder.
- Hard tablet with high binder: long Disintegration time.

B] Manufacturing / Processing variables

- **Excipients** – non active contents
- **Manufacturing processes**-
- Solid dosage form
- Method of granulation
  Wet granulation: faster dissolution
  APOC : agglomerative phase of communition
- Compression force
  Direct compression: faster dissolution
- Intensity of packing of capsule contents

- Intensity of packing of capsule contents
- Can inhibit or promote dissolution.
- Diffusion of GI fluids in to tightly packed capsules creates high pressure within capsule resulting in rapid burst & dissolution of contents.
- Capsule with finer particles & intense packing have poor release & low dissolution rate due to low pore size & poor penetrability by GI fluids.

C] Pharmaceutical ingredients / Excipients (formulation factors)

- Excipients are added to ensure

1. Acceptability
2. Physicochemical stability during shelf life
3. Uniformity of composition and dosage
4. Optimum bioavailability and functionality of drug product

- Commonly used excipients in various dosage forms

1. Vehicle- major component of liquid, oral and parenteral dosage form
2. Diluents – commonly added to tablet and capsule formulations to produce the necessary bulk
3. Binders and granulating agents – used to hold powders together to form granules or promote cohesive compact for directly compressible materials and to ensure that tablet remains intact after compression

4. Disintegrants – agent overcome the cohesive strength of the tablet (mostly hydrophillic)
5. Lubricants – added to tablet formulation to aid flow of granules

6. Coatings – Deleterious effects of various coatings on drug dissolution

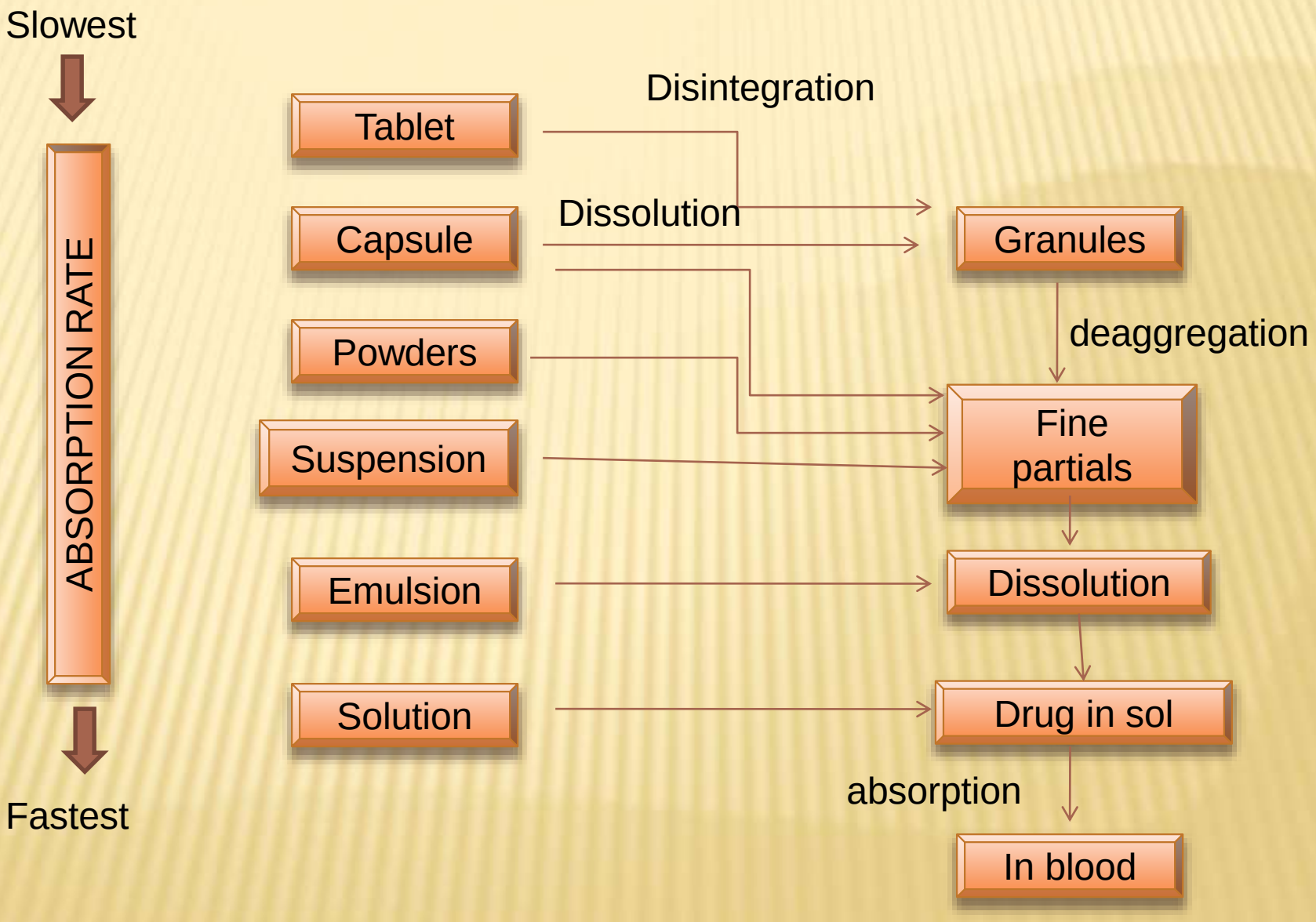
Enteric coat> sugar coat> non enteric coat

7. Suspending agents – Primarily stabilize solid drug particles by reducing their rate of settling through an increasing viscosity of medium
8. Surfactants – As wetting agents, solubilisers, emulsifiers, etc..

9. Buffers – Creating right atmosphere for drug dissolution
10. Complexing agents – To alter the physicochemical & biopharmaceutical properties of a drug
11. Colourants – Inhibitory effect on dissolution rate of several crystalline drugs

D] Nature & type of dosage form

The more complex a dosage form, greater the number of rate limiting steps and greater the potential for bioavailability problems


Slowest
ABSORPTION RATE
Fastest
Tablet
Capsule
Powders
Suspension
Emulsion
Solution
Disintegration
Dissolution
Granules
deaggregation
Fine partials
Dissolution
Drug in sol
absorption
In blood

Patient related factors

A] Age

	Infants	Adults	Elderly
Gastric pH	High	Normal[2 - 3]	High
Intestinal surface area	Low	More	Low
Blood flow to GIT	Low	Normal	Low
Absorption	Altered pattern	Normal	Impaired

B] Gastric emptying

Passage of drug after dissolution from stomach to small intestine

Rapid gastric emptying is advisable

1.Rapid onset of action is desired – Sedatives

2.Dissolution of drug occurs in intestine- Enteric coated tablets

3.Drugs not stable in gastric fluid – Penicillin G & erythromycin

4. Drugs absorbed from distal part of intestine- Vitamin B 12

Delay in gastric emptying is recomended

1. Food promotes drug dissolution & absorption – Griseofulvin
2. Disintegration & dissolution of dosage form is promoted by gastric fluids
3. Drugs dissolve slowly- Griseofulvin
4. Drugs irritate gastric mucosa- Aspirin , phenylbutazone & nitrofurantoin
5. Drugs absorbed from proximal part of small intestine – Vitamin B & C

Factors influencing gastric emptying

1. Volume of meal – Larger bulk longer gastric emtpying time
2. Composition of meal – Rate of gastric emptying: Carbohydrates>Proteins > Fats
3. Physical state & viscosity – Liquid meals (hour to empty) >solid meals (6 to 7 hrs)
4. Temperature of meal high or low temperature of ingested (in comparison with to body temperature) reduce gastric emptying

5. Gastrointestinal pH- Less acidic pH of stomach promotes gastric emptying while more acidic pH retards
6. Electrolytes – Water isotonic solutions , solutions empty stomach rapidly whereas a higher electrolyte concentration decreases gastric emptying
7. Body posture –Gastric emptying favoured while standing and lying on right side and vice versa
8. Emotional state – Stress & anxiety promotes while depression retards it
9. Exercise -Vigorous physical activity retards

	Retard gastric emptying	Promote gastric emptying
10.Disease states	❑ Gastroenteritis ❑ Gastric ulcer ❑ Pyloric stenosis ❑ Diabetes ❑ Hypothyroidism	❑ Partial or total gastrectomy ❑ Duodenal ulcer ❑ Hyperthyroidism
11. Drugs	❑ Poorly soluble antacids ❑ Anticholinergics ❑ Narcotic analgesics ❑ Tricyclic antidepressants	❑ Metoclopromide ❑ Domperidone ❑ Cisapride

C] Intestinal transit

- Small intestine is major site for drug absorption :Long intestinal transit time is desired for complete drug absorption.
- Residence time depends upon intestinal motility or contraction.
- Peristaltic contraction promote drug absorption by increasing the drug intestinal membrane contact, by enhancing drug dissolution.

Delayed intestinal transit is desirable for:

- Drugs that release slowly (sustained release)
- When the ratio of dose to solubility is high. (chlorthiazide)
- Drugs that dissolve only in intestine (enteric coated)
- Drugs which are absorbed from specific site in the intestine (Lithium carbonate, Vitamin B)
- When drug penetrate the intestinal mucosa very slowly (e.g. acyclovir)
- When absorption of drug from colon is minimal.

C] GI pH influence in several ways:

1.Disintegration:

- Disintegrating of some dosage forms is pH sensitive, enteric coated tabs dissolve only in alkaline pH.

2.Dissolution:

- A large no. of drugs either weak acids or weak bases, their solubility is greatly affected by GI pH.
- -weakly acidic drugs dissolve rapidly in alkaline pH.
- -basic drugs soluble in acidic pH..

3.Absorption:

- Depending upon drug pKa whether its an acidic or basic drug the GI pH influences drug absorption.

4.Stability of drug:

- GI pH influence the stability of drug. Eg; erythromycin

D] Blood flow to GIT

GIT is extensively supplied by blood capillary, about 28% of cardiac output is supplied to GIT portion, most drug reach the systemic circulation via blood only.

Any factor which affects blood flow to GIT may also affect absorption.

D] Disease state

Several disease state may influence the rate and extent of drug absorption.

Three major classes of disease may influence bioavailability of drug.

- **GI diseases**
- **CVS disease**
- **Hepatic disease**

GI DISEASES

- Achlorhydria : Decreased gastric emptying and absorption of acidic drugs like aspirin
- Malabsorption syndrome and celiac disease :

  decreased absorption
- Infections like shigellosis, cholera, food poisoning : ⇩ Absorption
- Gastrectomy may cause drug dumping in intestine, osmotic diarrhea and reduce intestinal transit time.

Cvs diseases

- In CVS diseases blood flow to GIT decrease, causes decreased drug absorption.

Hepatic diseases

- Disorders like hepatic cirrhosis influences bioavailability of drugs which under goes first pass metabolism.
- E.g. propranalol

E] Gastro intestinal contents

1.Food- drug interaction: In general presence of food either delay, reduce, increase or may not affect absorption.

Delayed	Decreased	Increased	Unaffected
Aspirin	Penicillin	Griesiofulvin	Methyldopa
Paracetamol	Erythromycin	Nitrofurantoin	Propylthiouracil
Diclofenac	Ethanol	Diazepam	sulphasomidine
Nitrofurontoin	tetracycline	Actively absorbed water soluble vit.	
Digoxin	Levodopa		
	Iron		

2. Fluid volume : high vol → better absorption e.g. erythromycin

3. Interaction of drug with normal GI contents:

bile salts : increases :lipid soluble drugs e.g. gresiofulvin

decreased : neomycin, kanamycin

4. Drug-Drug interaction in the GIT:

(A) Physico chemical drug- drug interaction:

Adsorption: Eg; anti diarrheal preparations contains adsorbents like kaolin, prevents a absorption of many drugs co-administered with them.

Complexation: Eg; calcium, aluminium salts decreases tetracycline

pH changes: Basic drugs changes gastric pH

E.g.; tetracycline with antacids

(B) Physiological interaction :

Decreased GI transit : Anticholinergics like propanthelin decrease GI transit and increased absorption of ranitidine and digoxin

Increase GI emptying : Metoclopramide increases GI motility and increased GI absorption of tetracycline , levodopa etc.

Altered GI metabolism : Antibiotics decrease bacterial metabolism of drug e.g. erythromycin increases efficacy of digoxin

F] First pass metabolism

- *" The loss of drug as it passes through GIT membrane, liver for the first time during the absorption process "*

- Four primary systems which affect pre systemic metabolism of a drugs.
  1. Luminal enzymes.
  2. Gut wall enzymes or mucosal enzymes.
  3. Bacterial enzymes.
  4. Hepatic enzymes.

- **Luminal enzymes:** These are enzymes present in gut fluids and include enzymes from intestinal and pancreatic secretions. E.g. hydrolases

- **Gut wall enzymes:** Also called mucosal enzymes they are present in gut and intestine, colon. E.g. alcohol dehydrogenase

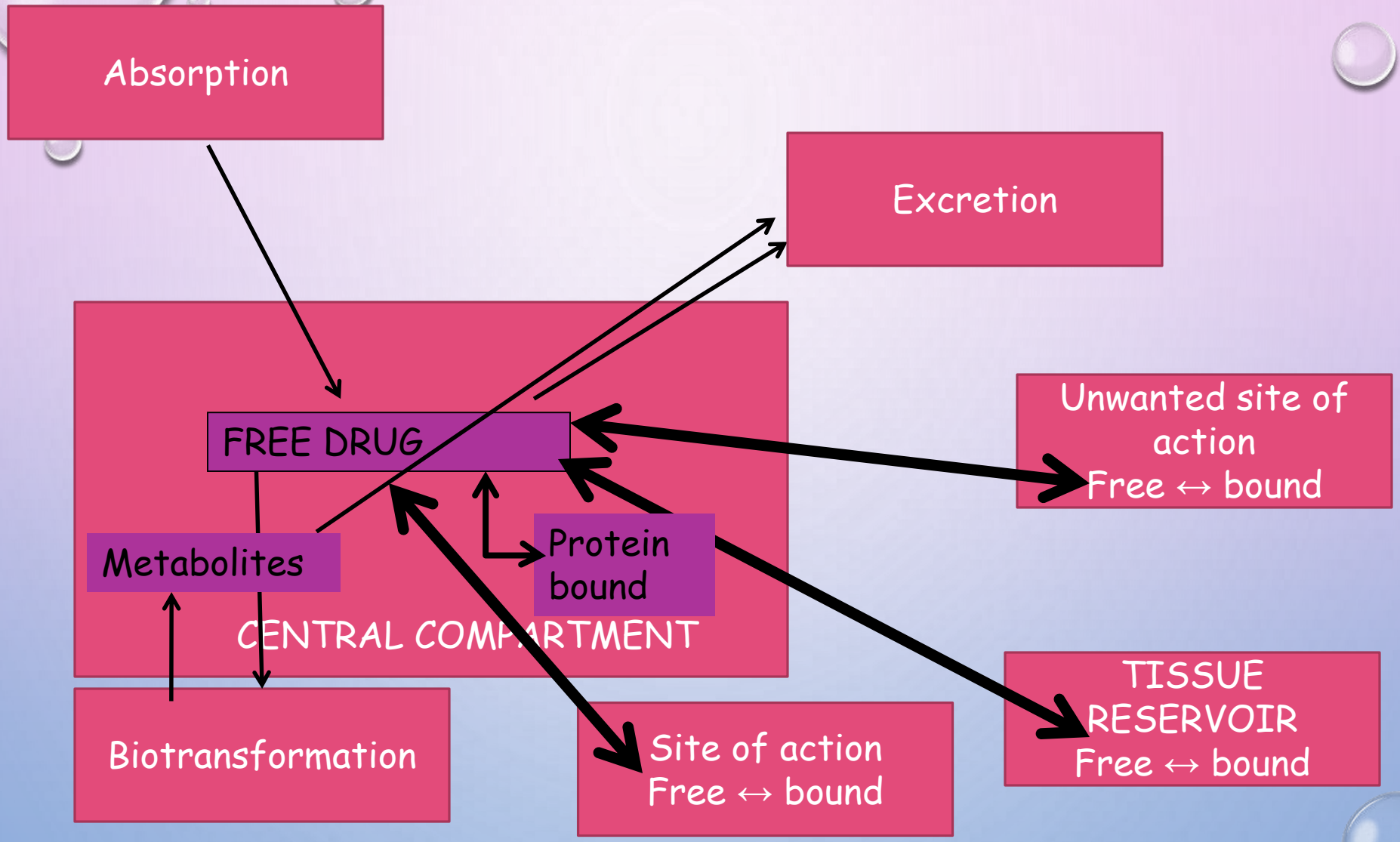
- **Bacterial enzymes:** GI microflora scantily present in stomach and small intestine and is rich in colon. e.g. sulphasalazine → sulphapyridine + 5 ASA

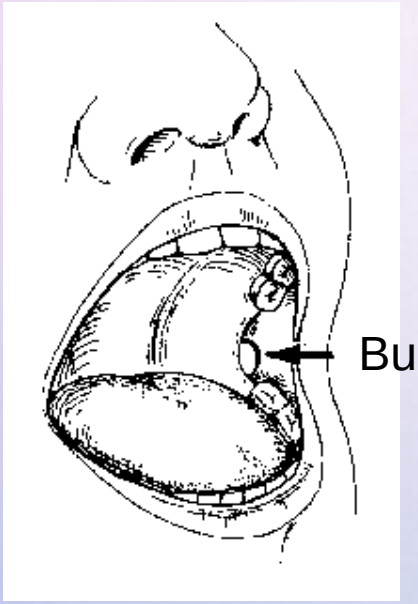
- **Hepatic enzyme:** several drug undergo first-pass hepatic metabolism, highly extracted ones being isoprenaline, nitroglycerin, morphine etc.

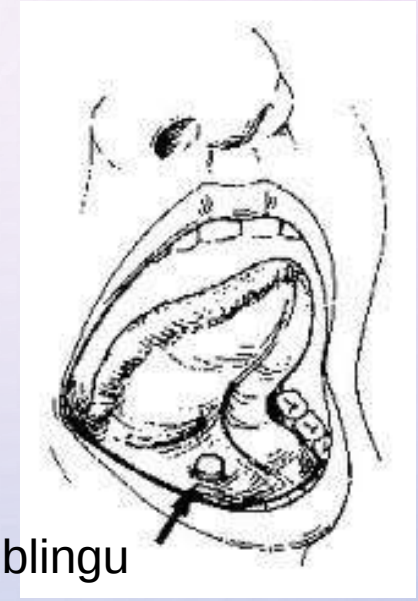
Summary

- Absorption is very important aspect of pharmacokinetic study of drug
- Knowledge of absorption helps us to decide route of administration
- Knowledge of absorption gives us idea about bioavailability of drug which in turn helps us in deciding dose
- Pharmaceutical industry utilises knowledge of absorption to prepare different formulation

ABSORPTION OF DRUGS FROM NON PER OS EXTRAVASCULAR ROUTES


Absorption
Excretion
FREE DRUG
Unwanted site of action
Free ↔ bound
Metabolites
Protein bound
CENTRAL COMPARTMENT
TISSUE RESERVOIR
Free ↔ bound
Biotransformation
Site of action
Free ↔ bound





Sublingual

Buccal/sublingual administration

Sublingual

- Drug is placed under tongue & is allowed to dissolve
- Passive diffusion

Buccal

- Medicament is placed between cheek & gum
- Passive diffusion

Advantages

Rapid absorption higher blood levels

- Useful for administration of antianginal drugs

No first –pass hepatic metabolism

Saliva facilitates drug dissolution & subsequent permeation as it keeps oral mucosa moist

Factors important in oral mucosal drug delivery

1) **Lipophilicity** - High lipid solubility required
2) **Salivary secretion** – Drug should be soluble in aqueous buccal fluids [biphasic solubility is necessary]
3) **pH of saliva** – Around 6, weakly acidic drugs are unionised at this pH and are easily absorbed

4) **Binding to oral mucosa** – Drugs that bind to oral mucosa bioavailability is poor

5) **Thickness of oral epithelium** - Sublingual absorption is faster than buccal since sublingual epithelium is thinner & immersed in larger volume of saliva

Q – drugs secreted in saliva ??

Ans-

1. Phenytoin
2. Lithium
3. Metronidazole
4. Rifampicin

Factors limit drug administration by this route

1. Limited mucosal surface
2. Taste of medicament
3. Discomfort [highly innervated area]
4. Irritant drugs can't be given
5. Drugs with high molecular weight

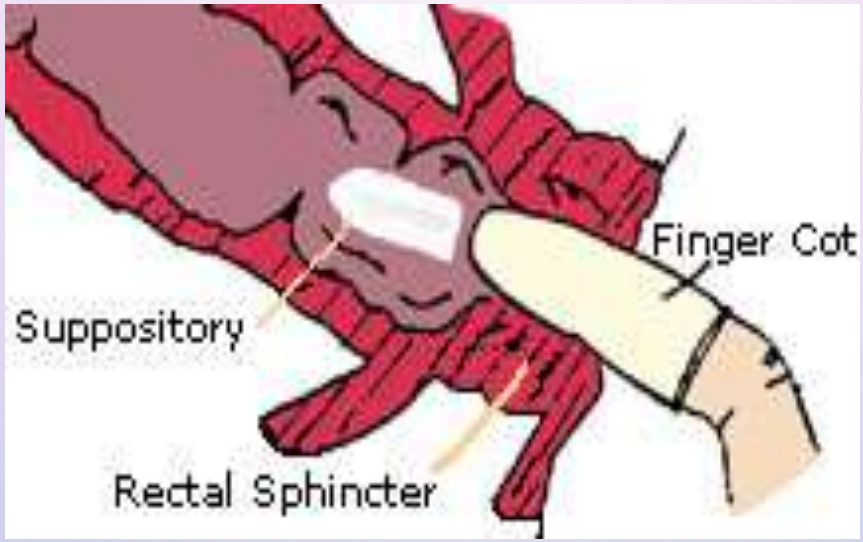
Examples

Antianginal → Nitrites & Nitrates

Analgesics→ Buprenorphine

Steroids like oestradiol & peptides like desaminooxytocin

Antihypertensives → Nifedipine



Rectal administration

Rectal administration

- Important route for children & geriatric patients
- Drugs administered as solution [micro enemas] and suppositories
- Absorption is rapid from solutions compared to suppositories
- Highly vascularised but slower absorption due to limited surface area

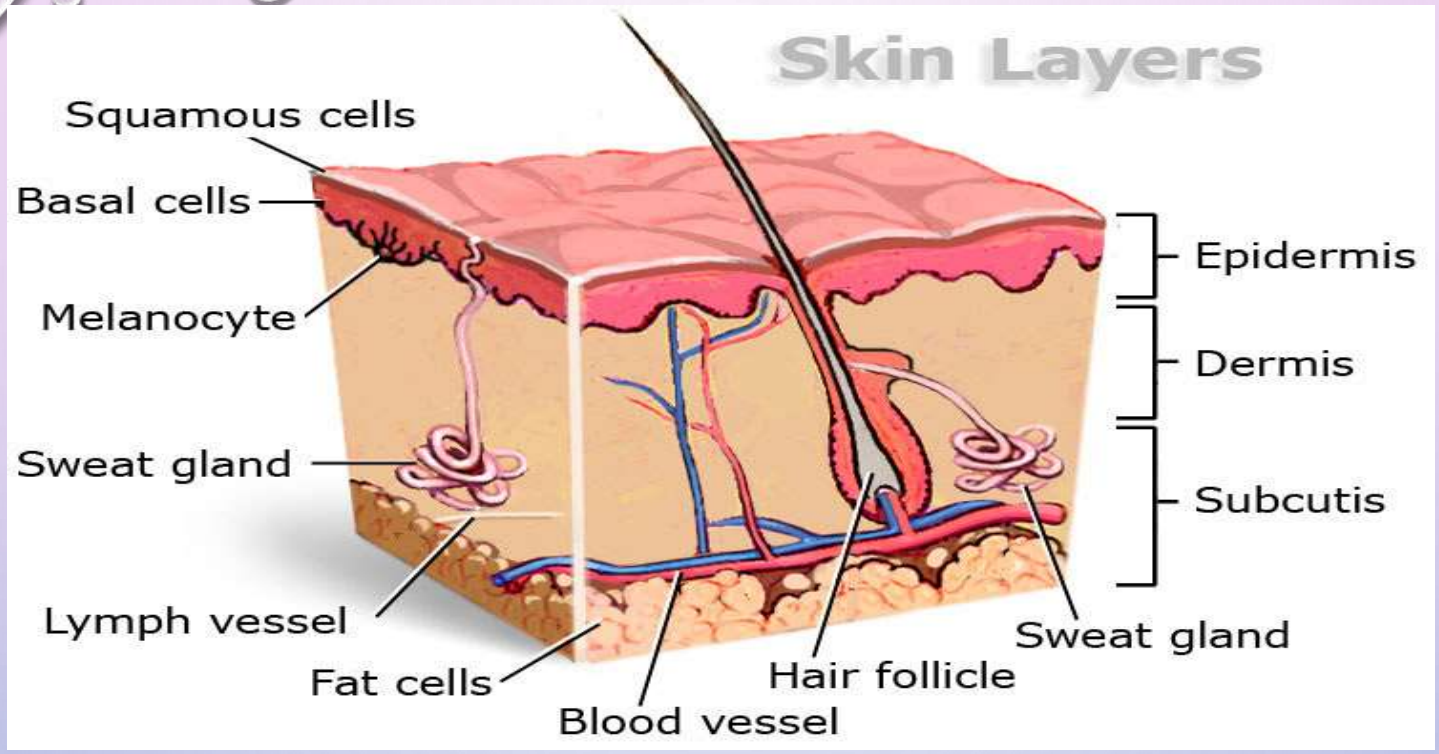
Rectal administration

Advantages	Disadvantages
Useful in patients having nausea & vomiting	Chances of rectal inflammation
50 % of drug bypasses 1st pass effect	Irritating suppositories promote defecation & drug loss
Useful for gastric irritant drugs	Limited surface area – slower absorption
Cyp 3A4 is present in lesser amount in lower intestine	Faecal matter retards absorption
	Inconvenient & embarrassing to patient

- **Examples** – Bisacodyl suppositories , diazepam prefilled syringes , glycerol ↓ to intracranial tension

- Q – differences between evacaunt & retention enema ??
- Ans

Evacuant enema	Retention enema
To remove fecal matter & flatus	For local action
E.G soap water enema	E.g prednisolone enema for ulcerative colitis
Volume – 600ml	Volume – 100 -120ml



Topical Administration

Skin

- Largest organ of body
- Weight 2kg & area 2 m^2
- 1/3rd of total blood circulating through body
- Skin is made up 3 distinct layers

1. Epidermis- Non vascular
2. Dermis- Highly vascular
3. Subcutaneous fat tissue

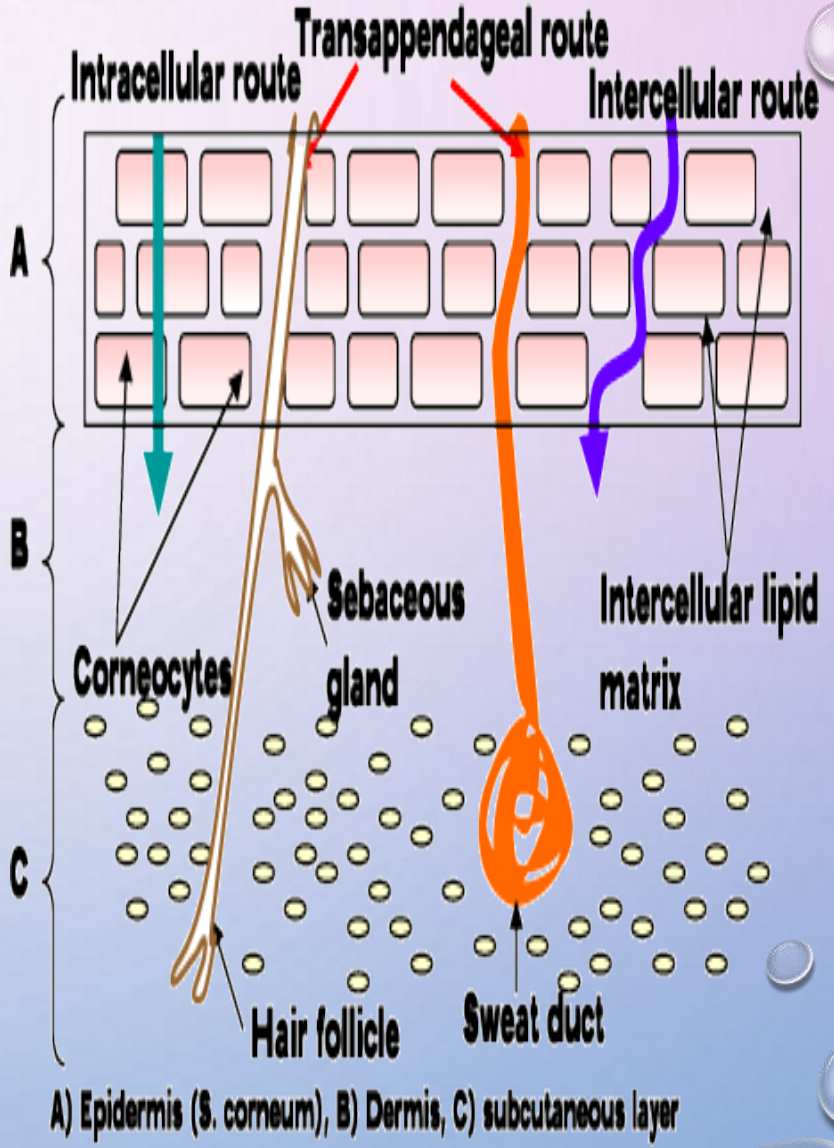
- Three pathways postulated for diffusion of solutes through skin

A. **Transcellular/ Intracellular** – passive diffusion

B. **Intercellular – Paracellular**

C. **Transappendageal** – Drug diffusion through

- Hair follicles
- Sweat glands
- Sebaceous glands



- Principal barrier to entry of xenobiotics is stratum corneum
- Factors that influence passive percutaneous absorption of drugs are

I. Skin conditions

II. Composition of topical vehicle

III. Application procedures or application conditions

A] Skin conditions

- **Thickness of stratum corneum** : Very slow from foot & palm (thickened stratum corneum)
- **Presence of hair follicles** : Rapid from Scalp (numerous hair follicles)
- **Trauma** : Destruction of stratum corneum promote absorption e.g. Cuts, rashses ,inflammation, mild burns

- **Hydration of skin** : Soaking of skin in water or occluding (using emollients, plastic film or dressing)promote hydration of skin and ↑drug absorption
- **Age** : Infants - Systemic toxicity is of particular concern

  Elderly - More prone allergic & irritant effects
- **Skin pH** : Normal 4-6

B] Composition of topical vehicle

- **Vehicle or base** :

In which drug is dissolved than dispersed promotes absorption

- **Permeation enhancers** :

Incorporation of chemicals like propylene glycol , azone promote absorption

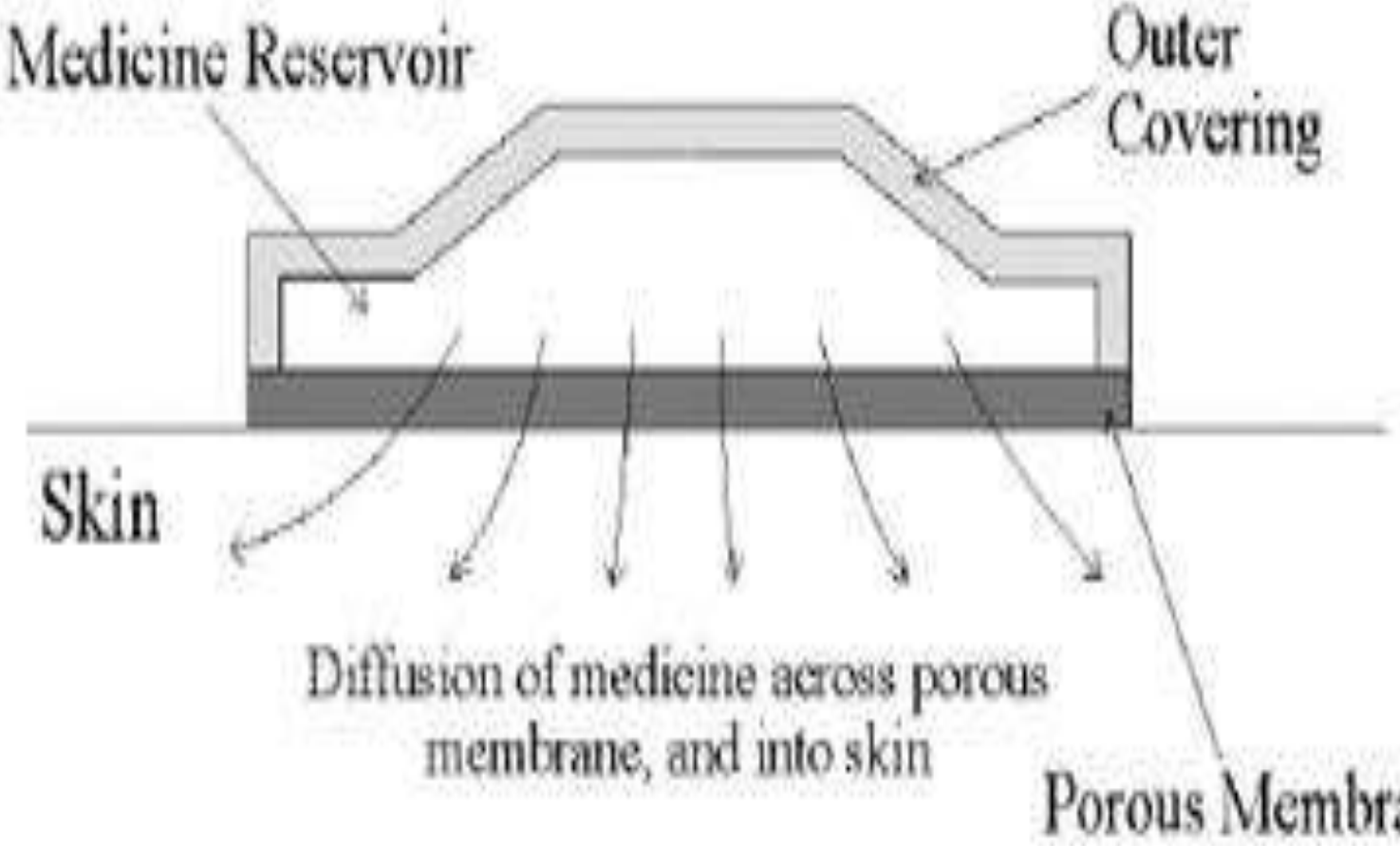
C] Application conditions

- **Rubbing** : ↑ blood circulation to area of application and thus ↑ drug permeation
- **Occlusion** : Trapped moisture endogenous or exogenous → hydrates stratum corneum → promotes drug permeation
- **Loss of vehicle** : Loss of vehicle ↓ transdermal permeation

Examples

- **Remain superficial** - Sunscreen , insect repellants , cosmetics
- **Delivery to appendages** – Anti- infective , antiacne , antiperspirants /hair removers
- **Delivery to local tissues** – Antimitotics , anti-inflammatories , antihistamines , anaesthetics
- **Systemic delivery** – Clonidine , scopolamine, nicotine , fentanyl , oestradiol

Transdermal Patch



Q – Where is transdermal patch applied ??

Ans –

1. Chest
2. Upper abdomen
3. Mastoid region

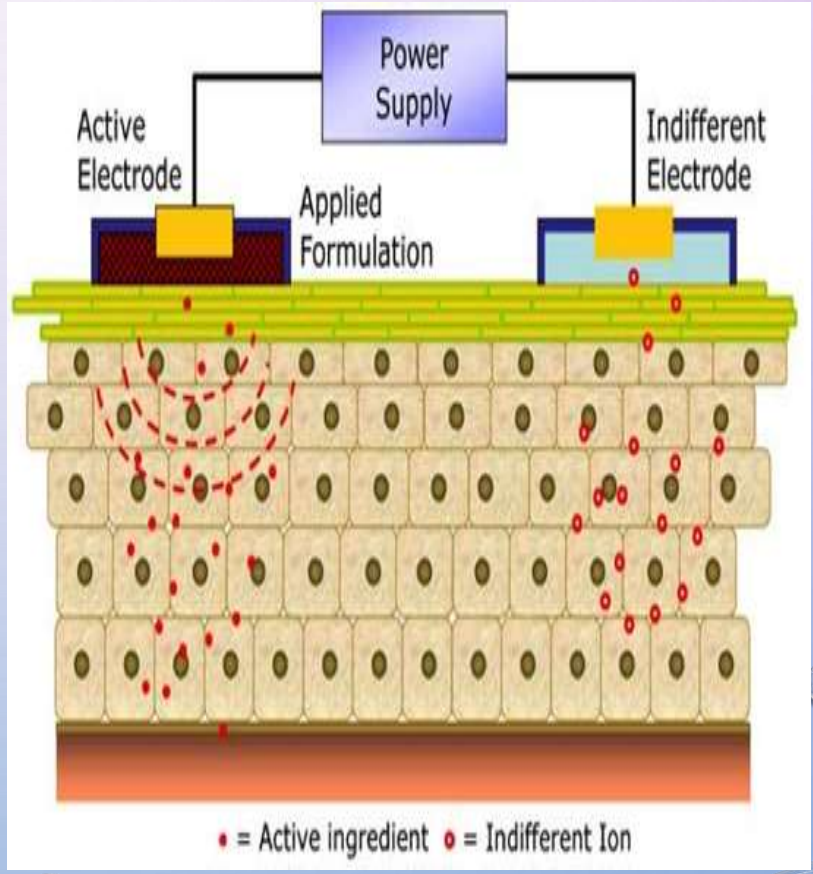
Transdermal drug delivery

Ionic drugs are not absorbed transdermally

- Iontophoresis

Delivery of ionic drug into body by means of electric current

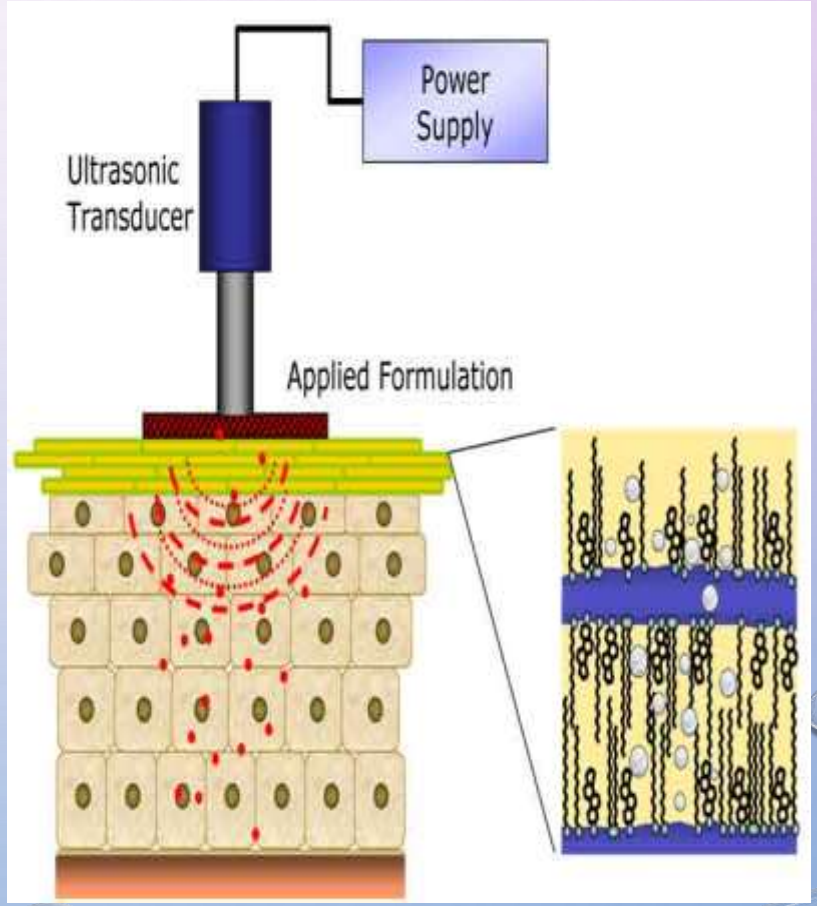
Examples cortisol , methacholine , lidocaine , salicylates , peptides delivered in this way



Transdermal drug delivery

- Phonophoresiss

Movement of drug molecules through skin under influence of ultrasound



- Inunction

Certain drugs when rubbed into skin (inunction) get absorbed & produce systemic effects e.g. nitroglycerine ointment in angina pectoris

- Jet injection (dermojet)

Transcutaneous introduction of drug by means of high velocity jet produced through microfine orifice

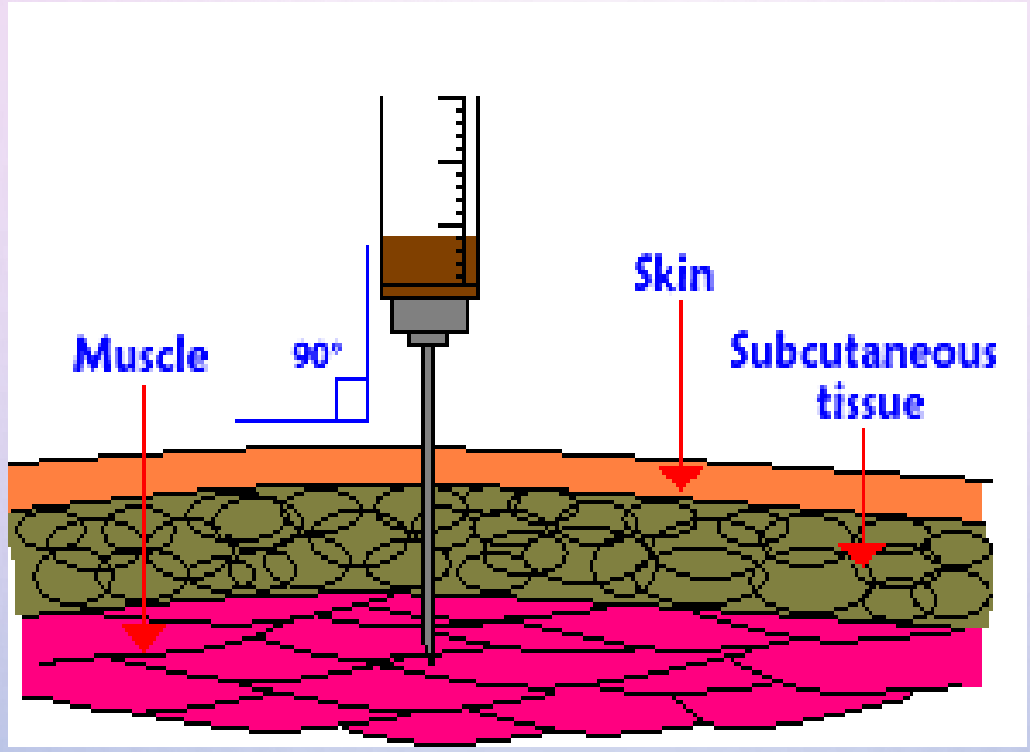
Essentially painless

- Pellets & biodegradable implants

Solid pellet or packed in biodegradable tubes

Implanted under skin

Example – Testosterone & contraceptive implants



Intramuscular injection

- Absorption from IM sites is rapid but slower in comparison to IV
- Factors that determine rate of absorption from im sites

A. **Vascularity of injection site** – Arm (deltoid) >Thigh (vastus lateralis) > Buttocks (gluteus maximus)

B. **Lipid solubility & ionisation of drug** - Highly lipophilic drug rapidly absorbed by passive diffusion & hydrophilic and ionised drug slowly through capillary pores

C. Molecular size – Small molecules & ions gain direct access to capillary & macromolecules taken up by lymphatic system

D. Volume of injection & drug concentration- Concentrated & large volume absorbed faster

E. Viscosity of injection vehicle

Viscous vehicles (vegetable oil) → Slow absorption (Depot injection)

Limitations – 1. Irritant drugs can't be given

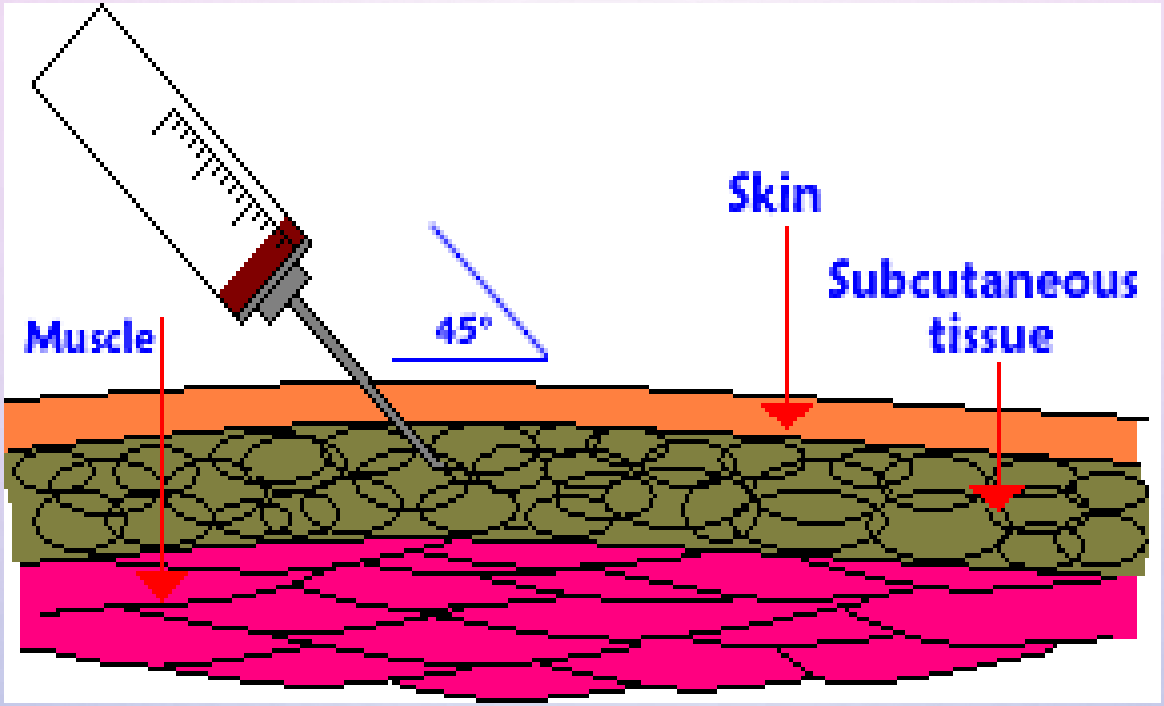
2. Large volume can't be given

(max 5 ml can be given)

3. Chances of abscess formation

4. Chances of nerve damage

- Q – In children where should IM injections be given ??
- Ans – on lateral aspect of thigh until child starts walking
- - when child starts walking gluteal muscle mass is very well developed after which IM injections can be given in buttocks



Subcutaneous injection

Subcutaneous

- Absorption - Slower than IM sites due to poor perfusion
- Used – 1. When slow response is desired

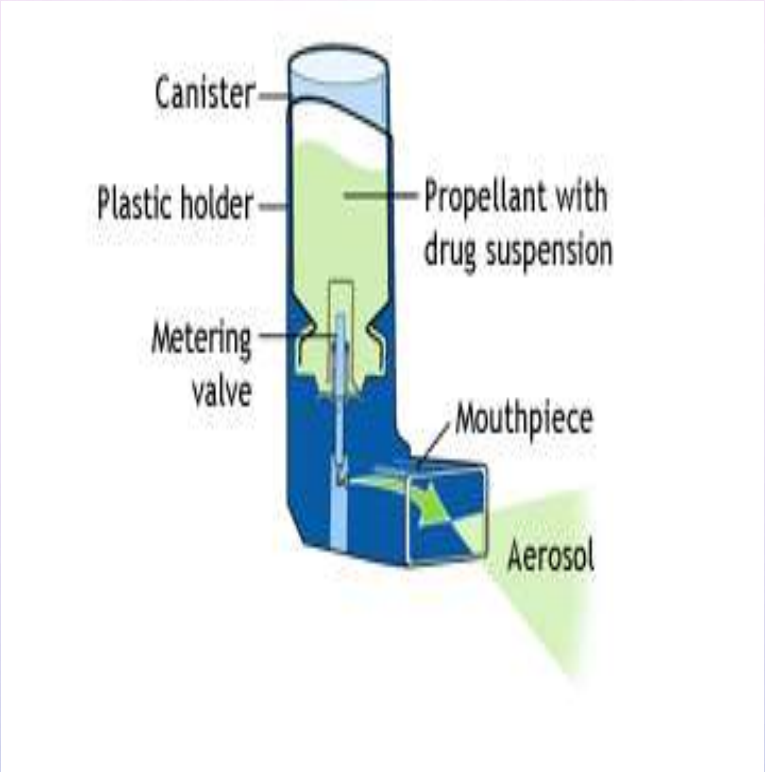
  2. Drug degrade when taken orally

Limitations – 1. Irritant drugs can't be given

2. Large volume can't be given(max -1ml)

Example - Insulin & low molecular weight heparin

- Q – Why vaccines are administered by subcutaneous route??
- Ans – Active protein reaches directly to lymphatic tissue without getting destroyed elsewhere in the body



Pulmonary administration

- Extremely rapid absorption due to
  - Large surface area of alveoli
  - High permeability of alveoli
  - Rich perfusion
- Depends upon
  - pH of pulmonary fluid
  - Particle size > 10 μ - NOT reach pulmonary tree
- Example – Oxygen, general anesthetics, salbutamol, beclomethasone, cromolyn sodium

Advantages	Disadvantages
Faster absorption hence quick onset of action	Bronchial irritation may lead to ↑ bronchial & salivary secretions
Avoidance of 1st pass effect	
Rate drug delivery can be controlled	
Self administration is possible	

Intranasal application

INTRANASAL

- Used for the systemic delivery of some peptides & protein drugs
- Used for treatment of local symptoms like nasal congestion , allergic rhinitis etc
- Rapid absorption due to rich vasculature and high permeability

- Faster rate –Drug high lipophilicity
- Factors - pH of nasal secretion, viscosity, and pathological conditions like common cold and rhinitis

Examples

- Desmopressin
- Oxytocin
- GnRH analogues
- Calcitonin
- Nasal decongestants

Intraocular administration

Intraocular administration

- Mainly for local effects such as mydriasis, miosis, anesthesia and glaucoma.
- Sterile aqueous solution of drug
- Cornea – Major barrier - both hydrophilic and lipophilic characters.
- Thus for optimum intra ocular permeation drug should posses biphasic solubility.

Examples

- Drugs used in glaucoma

1. Miotics – Pilocarpine
2. Non selective ß blocker - Timolol
3. $PGF_{2\alpha}$ - Latanoprost

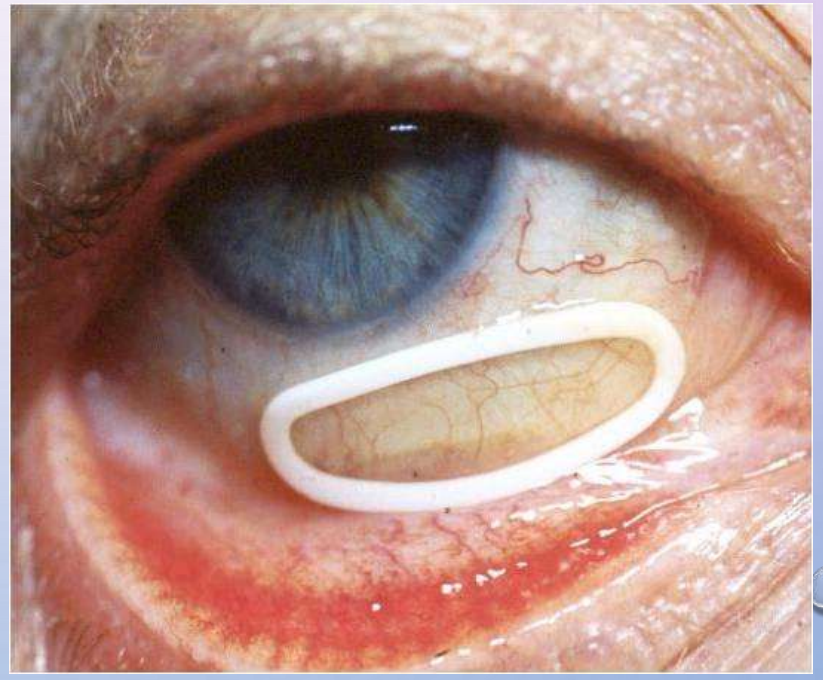
Q – Why latanoprost has become drug of choice in glaucoma??

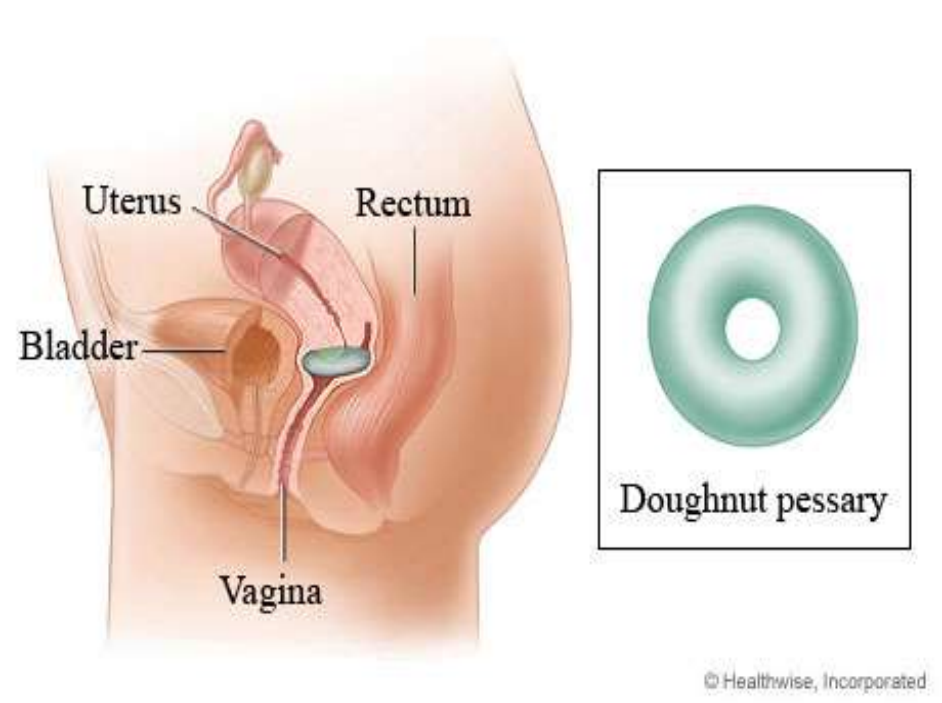
Ans –

1. Latanoprost is non irritant
2. ↑ Uveo scleral outflow

Occuserts

- Elliptical micro units (drug reservoir)
- Drug -delivered slowly at steady rate
- Example – pilocarpine occuserts

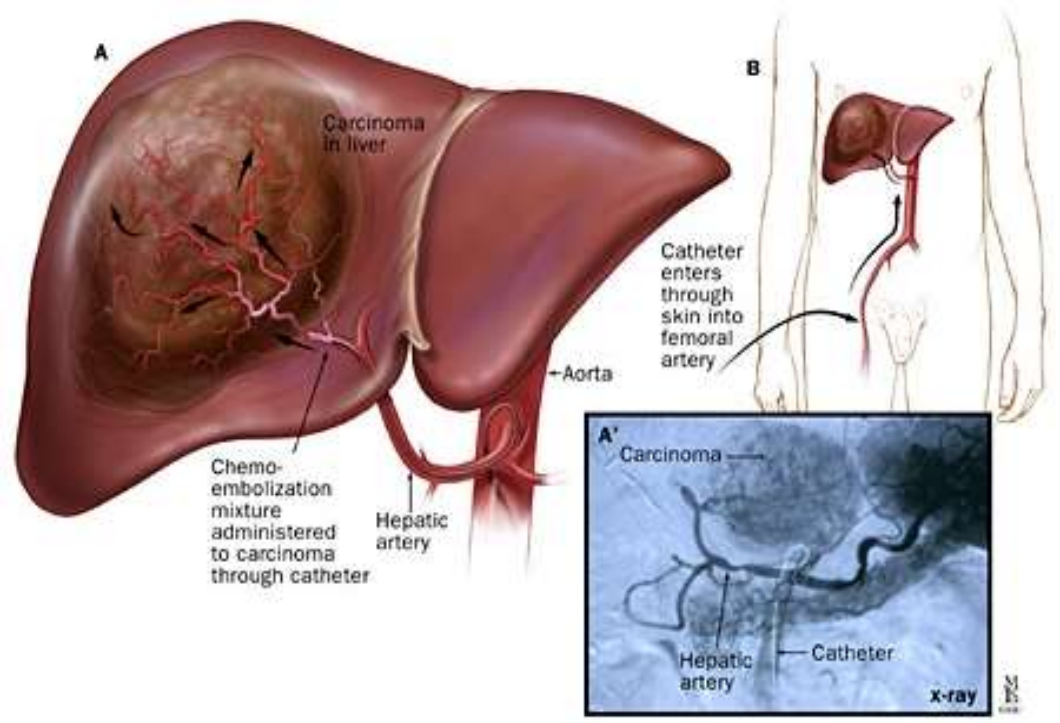




Vaginal administration

VAGINAL ADMINISTRATION

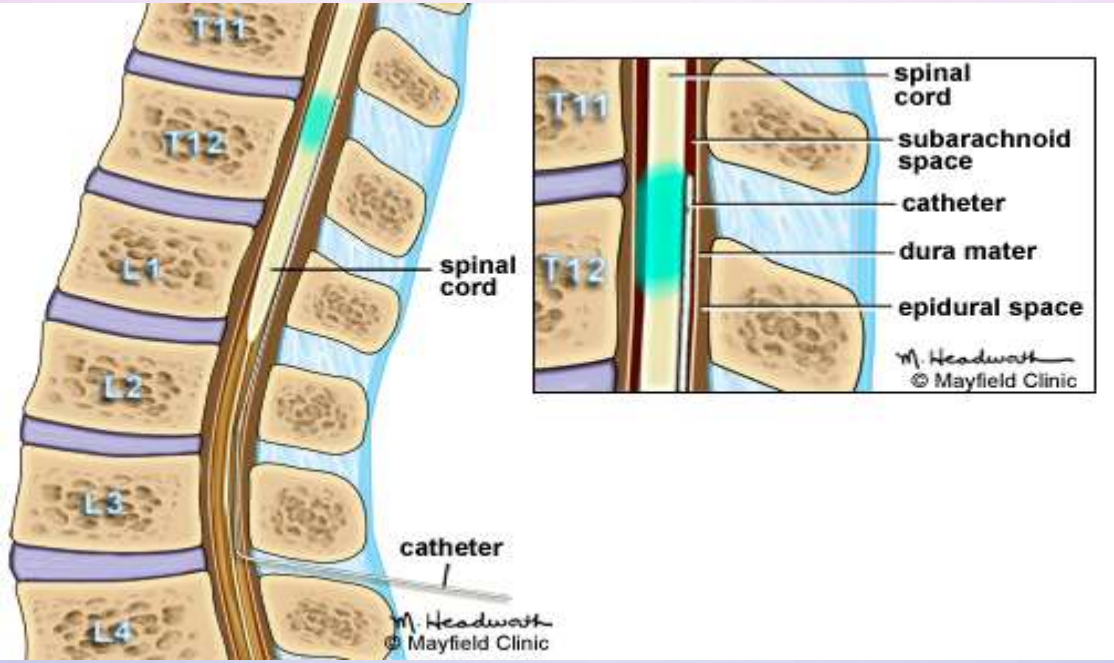
- Intended to act locally e.g. Infection, contraception
- Factors affecting drug absorption are
  - -pH of the lumen fluid 4-5.
  - -Vaginal secretions.
  - -Microbes at vaginal lumen
- Examples - Pessaries of sulfa drugs , antifungal & metronidazole



Intraarterial administration

INTRARTERIAL ADMINISTRATION

- Localized drug effect
- Used in treatment liver tumors , head and neck cancers
- Diagnostic purpose- coronary angiography & cerebral angiography (radiopaque contrast media)



Intrathecal administration

Intrathecal administration

- Local rapid effects of drugs on meninges and cerebro spinal axis
- Limitation – strict aseptic condition & great expertise is required
- Examples . Spinal anesthesia, acute CNS infections (amphotericin –B), brain tumor,

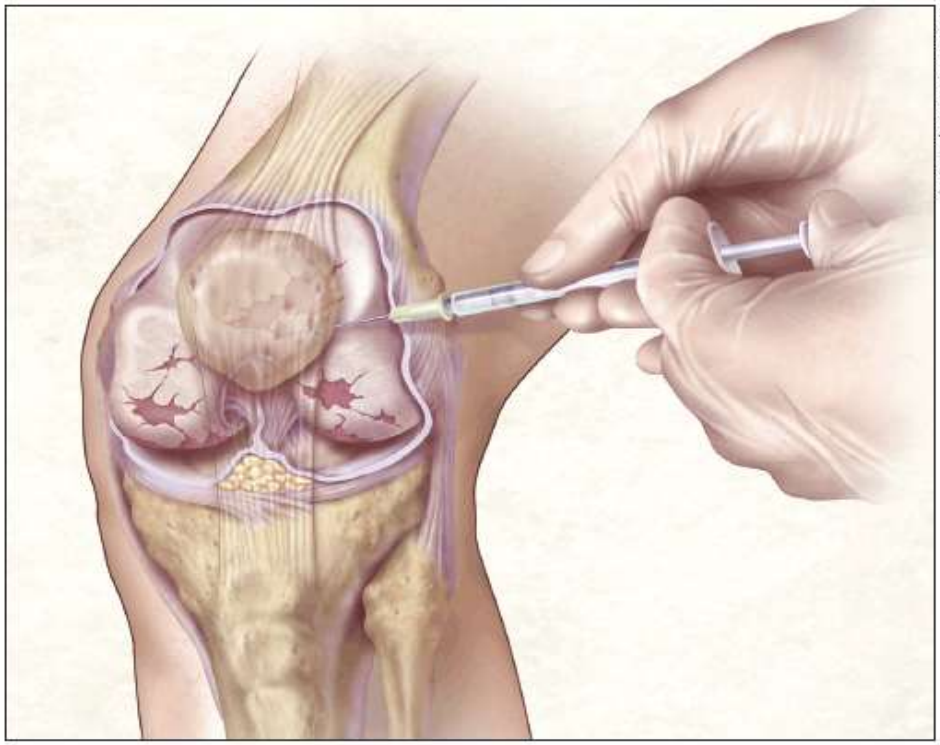


Figure – Several palpation-based, anatomical landmark–guided approaches for the administration of therapeutic injections into the knee have been described, including the extended leg lateral midpatellar (LMP) and medial midpatellar portals and the bent leg anteromedial and anterolateral portals. In one study, the LMP approach was significantly more accurate than the other approaches studied.

Intraarticular administration

Intraarticular administration

- Drugs are administered in joint space
- To attain high local concentration
- For treatment of local conditions like rheumatoid arthritis
- Limitation

1) Expertise required
2) Strict aseptic precaution required
3) Repeated administration might further damage joint

Example – Hydrocortisone or gold chloride

Conclusion

- The knowledge of pharmacokinetics of a drug helps us to understand which route should be preferred for a particular drug

A. To achieve better bioavailability

B. To achieve better efficacy

C. To avoid adverse effects

References

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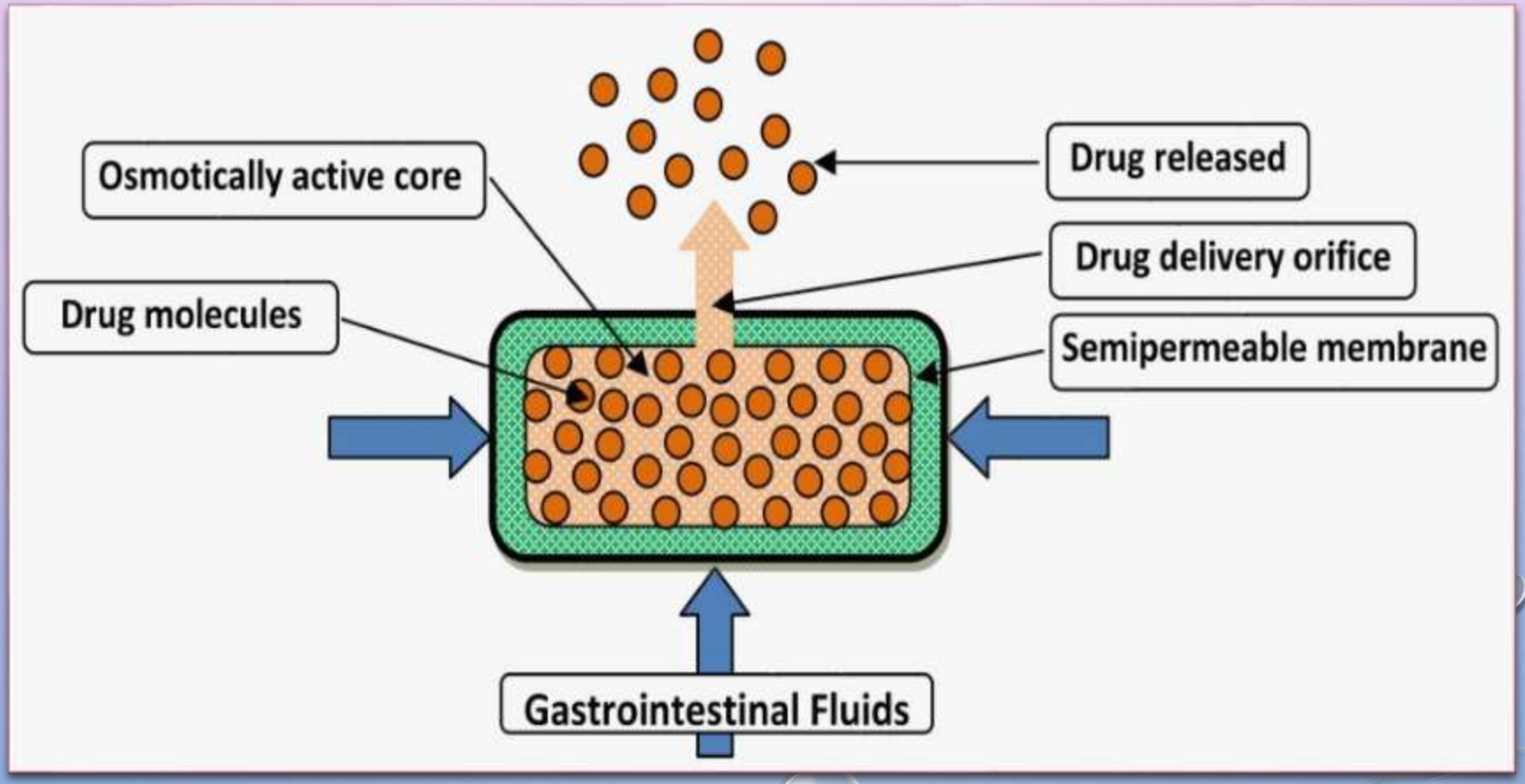
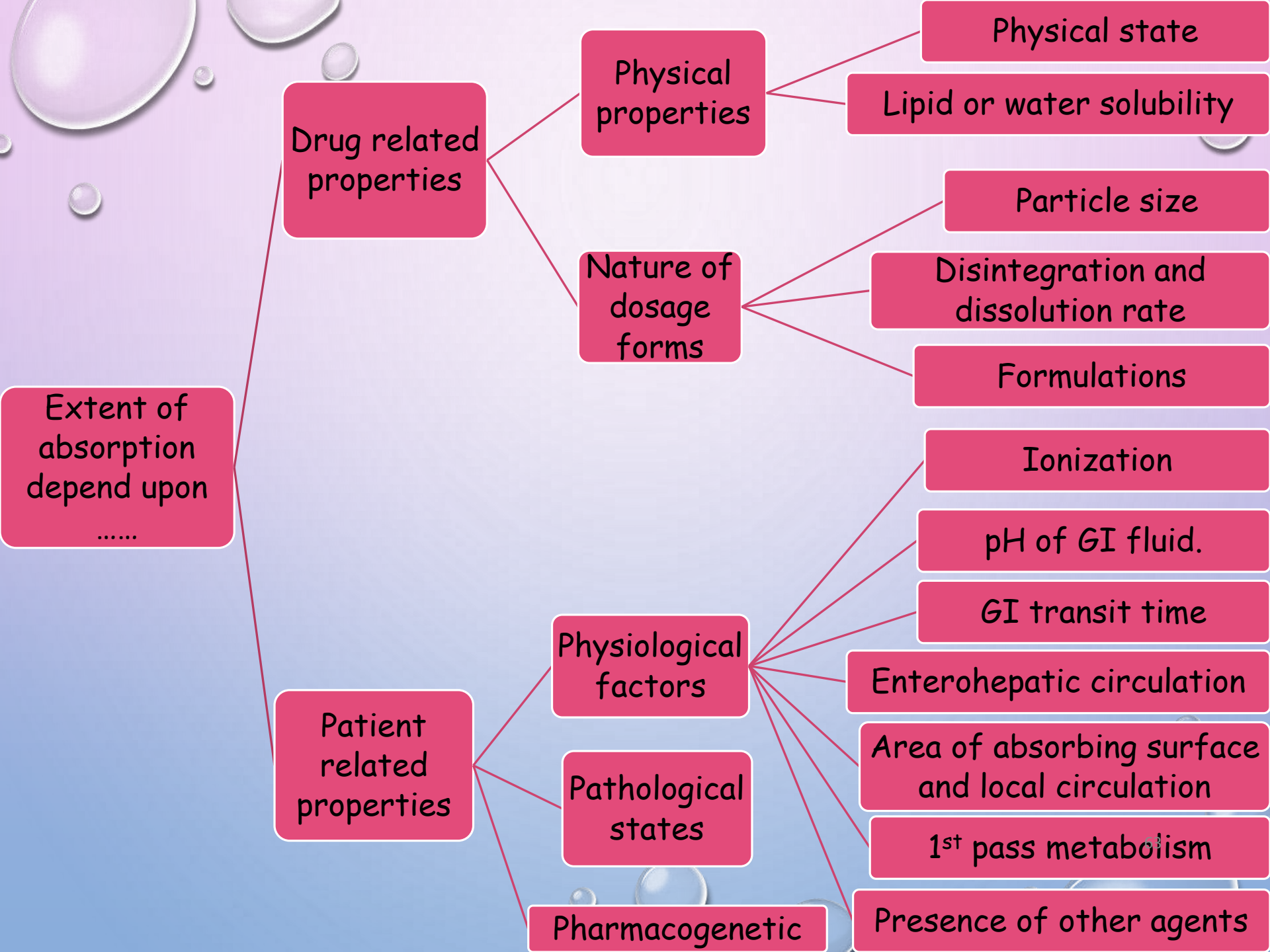
- Biopharmaceutics and pharmacokinetics a treatise 2nd edition by D. M. Brahmankar and Sunil B. Jaiswal


Thank
You

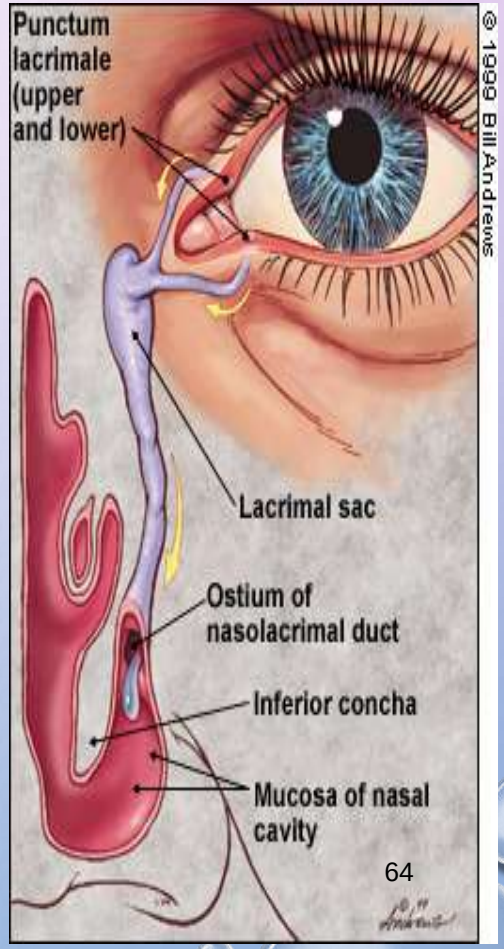
Oral osmotic drug delivery




Extent of absorption depend upon ……
Drug related properties
Physical properties
Physical state
Lipid or water solubility
Nature of dosage forms
Particle size
Disintegration and dissolution rate
Formulations
Patient related properties
Physiological factors
Ionization
pH of GI fluid.
GI transit time
Enterohepatic circulation
Area of absorbing surface and local circulation
1st pass metabolism
Presence of other agents
Pathological states
Pharmacogenetic

Factors affecting absorption

1. pH of lachrymal fluid : weak electrolytes like pilocarpine
2. pH of fomulation :
   - High pH - ↓ lacrimation -↑ absorption
   - Low pH - ↑ lacrimation - ↓ absorption
3. Rate of blinking : ↑ lacrimation - ↓ absorption
4. Volume of instillation : optimal
5. Concentration of drug : ↑ concentration →↑
6. Viscosity : Better due to longer contact time



Q – Intramedullary administration

Ans –

- Injection into tibial or sternal bone marrow..
- Eg - bone marrow transplantation

Steroid

Route	Inhalational	Topical	Occular	Intrarticular
	Budesonide	Clobetasol	Fluoromethalone	Betamethasone
	Beclomethasone	Clocortolone	Medrysone	Methylprednisolone
	Fluticasone	Amcinonide		Triamcinolone
	Mometasone	Desonide		
	Triamcinolone	Flucinolone		
		Alclometasone		
		Dexsoximetasone		

- Both topical / inhalational steroids – fluticasone & beclomethasone