TOPICAL DRUG DELIVERY

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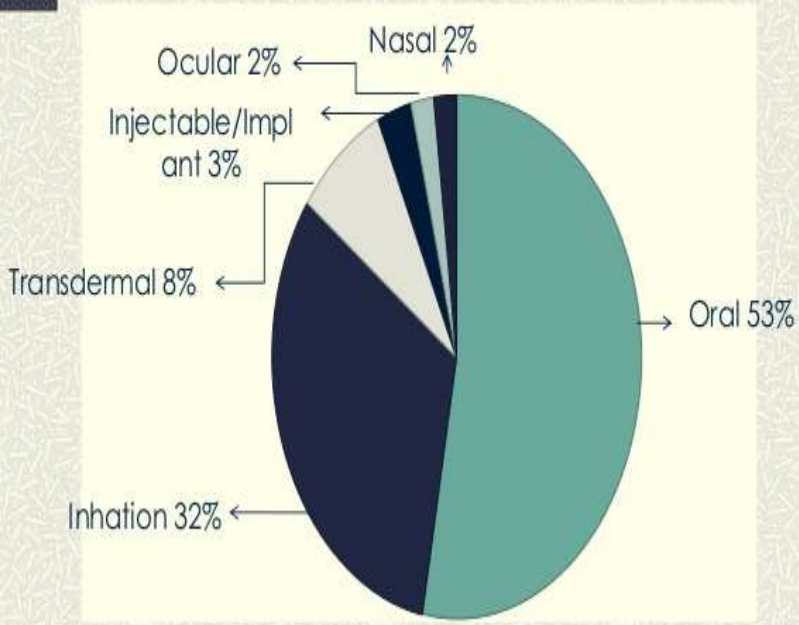
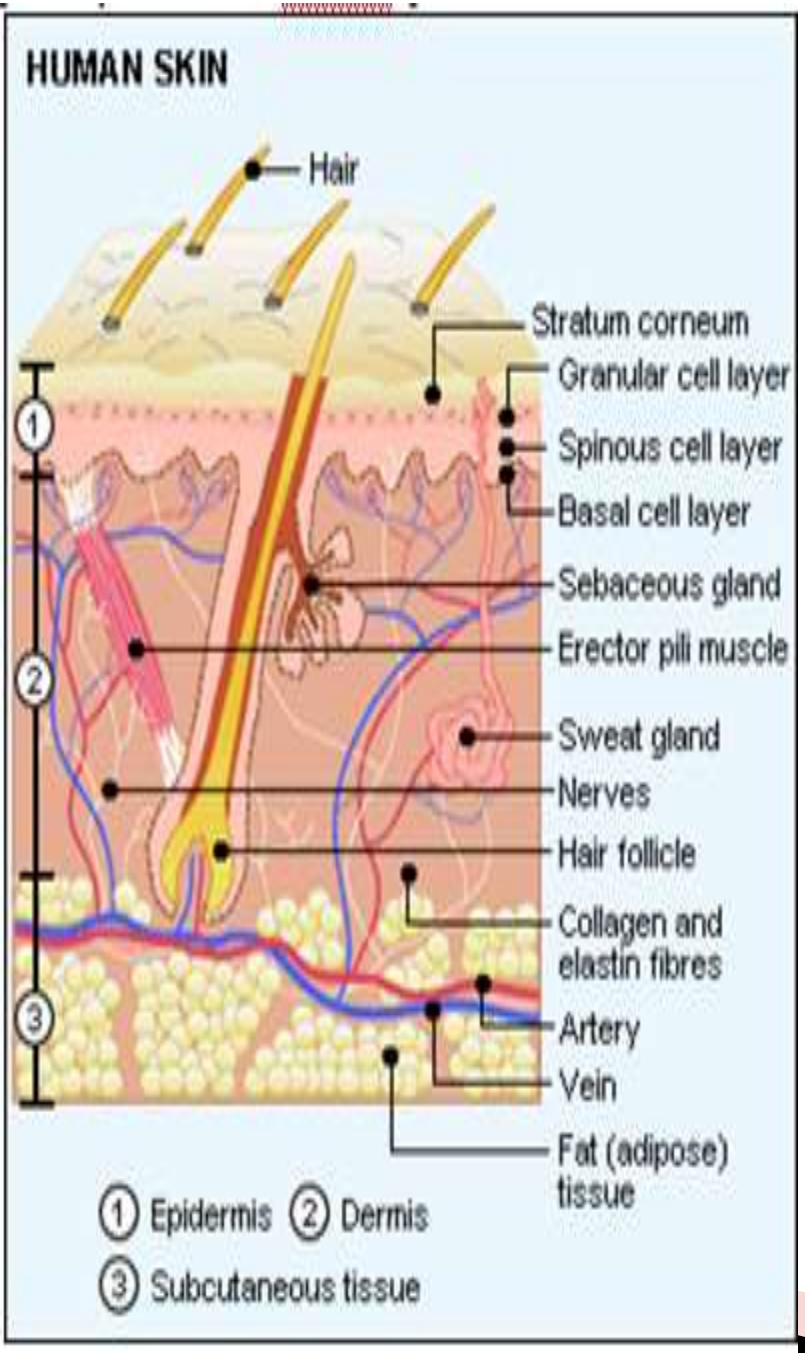
DRUG DELIVERY STSTEM

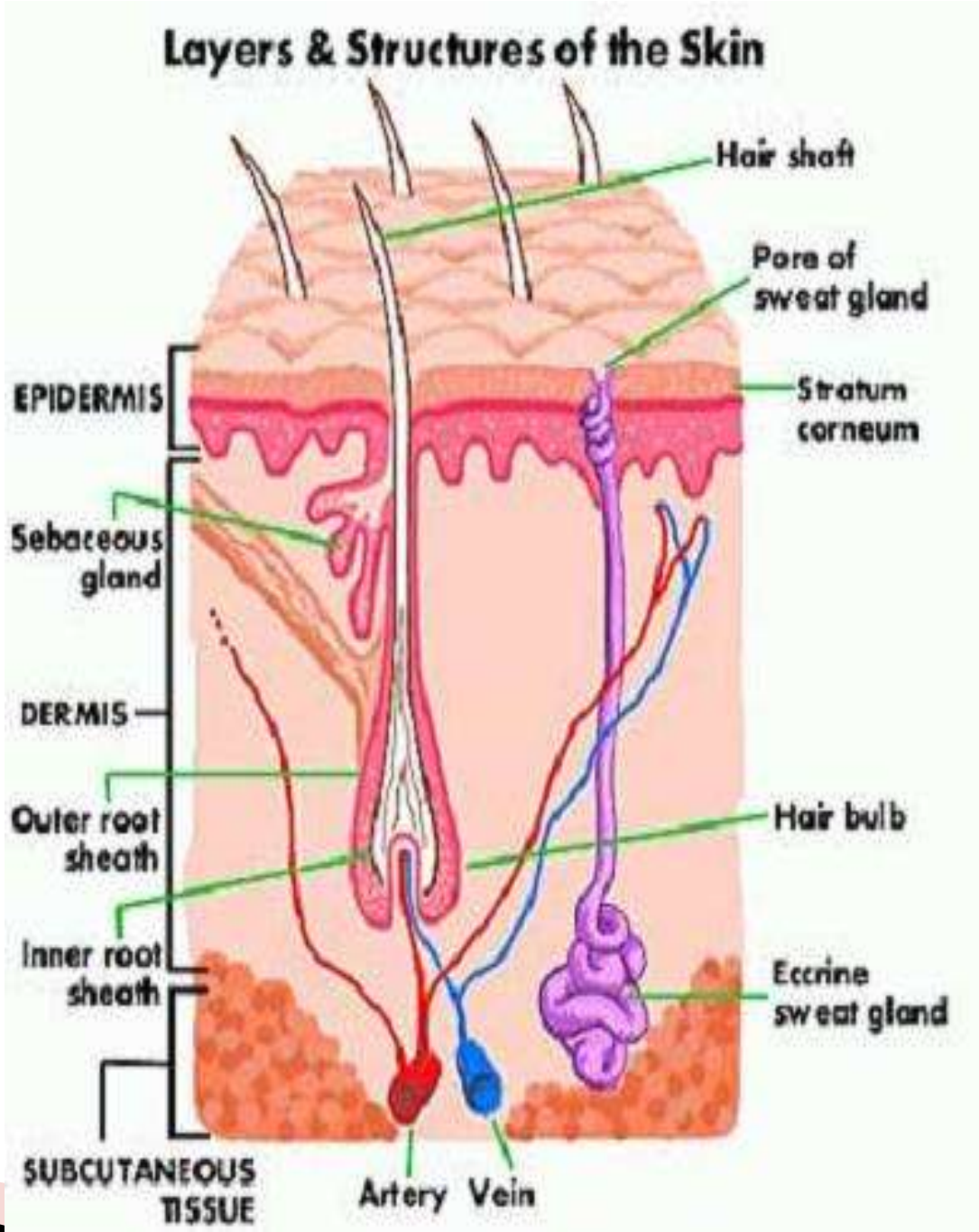
- Oral
- Inject-able
  - Needle
  - Needle-less
- Mucosal
  - Nasal
  - Buccal
  - Pulmo-nary
- Topical
- Trans-dermal
  - Active
  - Passive
- Ocular
- Vaginal/ Anal

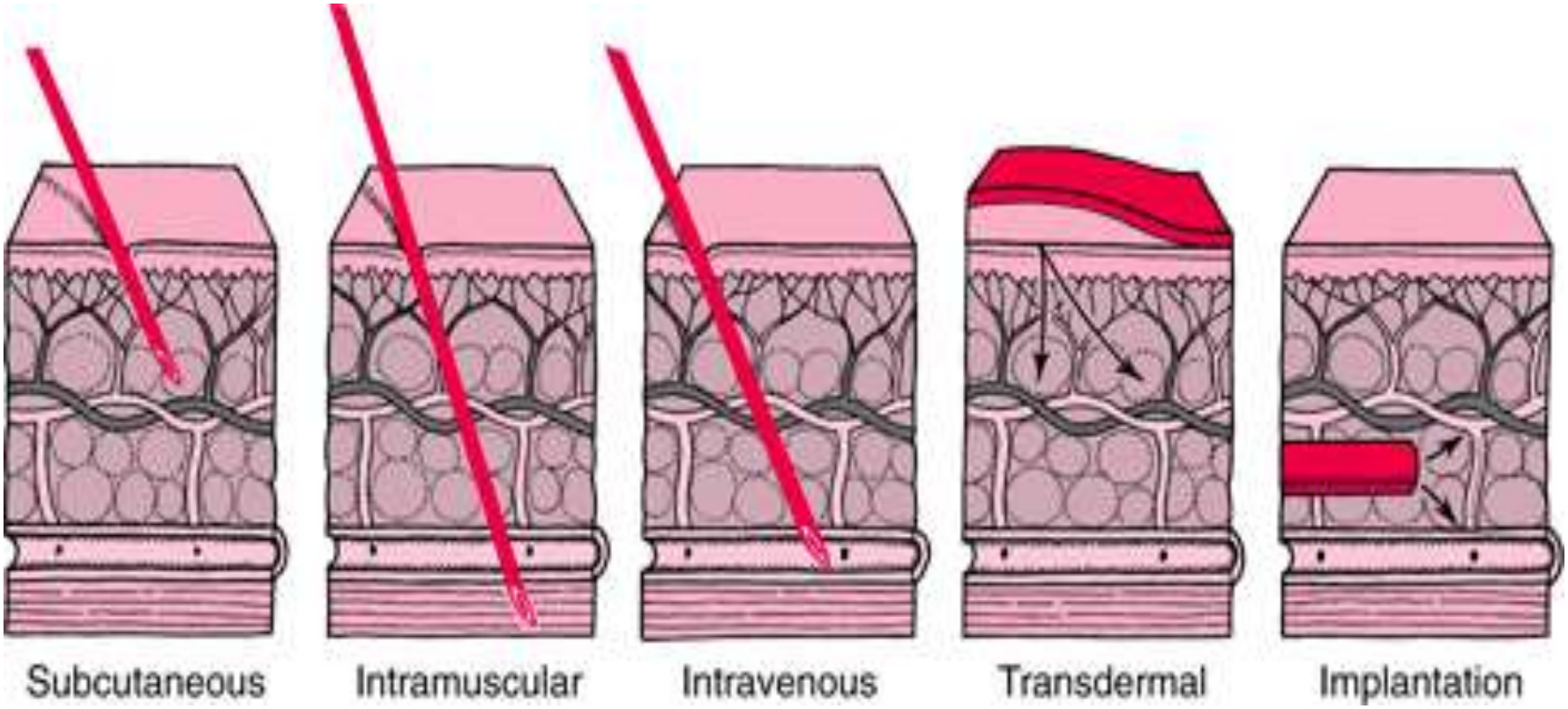
GLOBAL DRUG DELIVERY MARKET BY ADMINISTRATION MODE



Dermatologic agent


HUMAN SKIN
Hair
Stratum corneum
Granular cell layer
Spinous cell layer
Basal cell layer
Sebaceous gland
Erector pili muscle
Sweat gland
Nerves
Hair follicle
Collagen and elastin fibres
Artery
Vein
Fat (adipose) tissue
1
2
3
1 Epidermis 2 Dermis
3 Subcutaneous tissue


Layers & Structures of the Skin
Hair shaft
Pore of sweat gland
Stratum corneum
EPIDERMIS
Sebaceous gland
DERMIS
Outer root sheath
Hair bulb
Inner root sheath
Eccrine sweat gland
SUBCUTANEOUS TISSUE
Artery
Vein


Subcutaneous
Intramuscular
Intravenous
Transdermal
Implantation

Pengobatan Topikal

Faktor yang mempengaruhi absorbsi perkutan

1. Konsentrasi obat
2. Makin luas → penyerapan >>
3. Afinitas bahan obat >> vehikulum
4. Vehikulum bersifat lemak → penghalang uap air
5. Hidrasi kulit → absorbsi perkutan
   Lama pemakaian → absorbsi >>

Faktor interaksi

1. Fc. biologik : umur regio
2. Fc. Fisiko kimia : obat – kulit
   vehikulum – kulit

Aplikasi Obat Topikal

1. Jumlah harus cukup (R/)
2. Compliance pasien
3. Resep generik

Regio ⟶ obsorbsi : penetrasi skrotum
> dahi > plantar pedis

Pengaruh Fisik dan Kimiawi

- Fisik
  - Mengeringkan
  - Membasahi
  - Melembutkan
  - Lubrikasi
  - Mendinginkan
  - Memanaskan
  - Melindungi
- Kimia
  - Anti alergik
  - Anti mikotik
  - Anti inflamasi

Pedoman TH/ Topikal

1. Basah dan basah → kompres
   kering dan kering → salep
2. akut → aktif lemah

Prinsip terapi topikal :

1. Vehikulum
2. Bahan aktif

VEHIKULUM

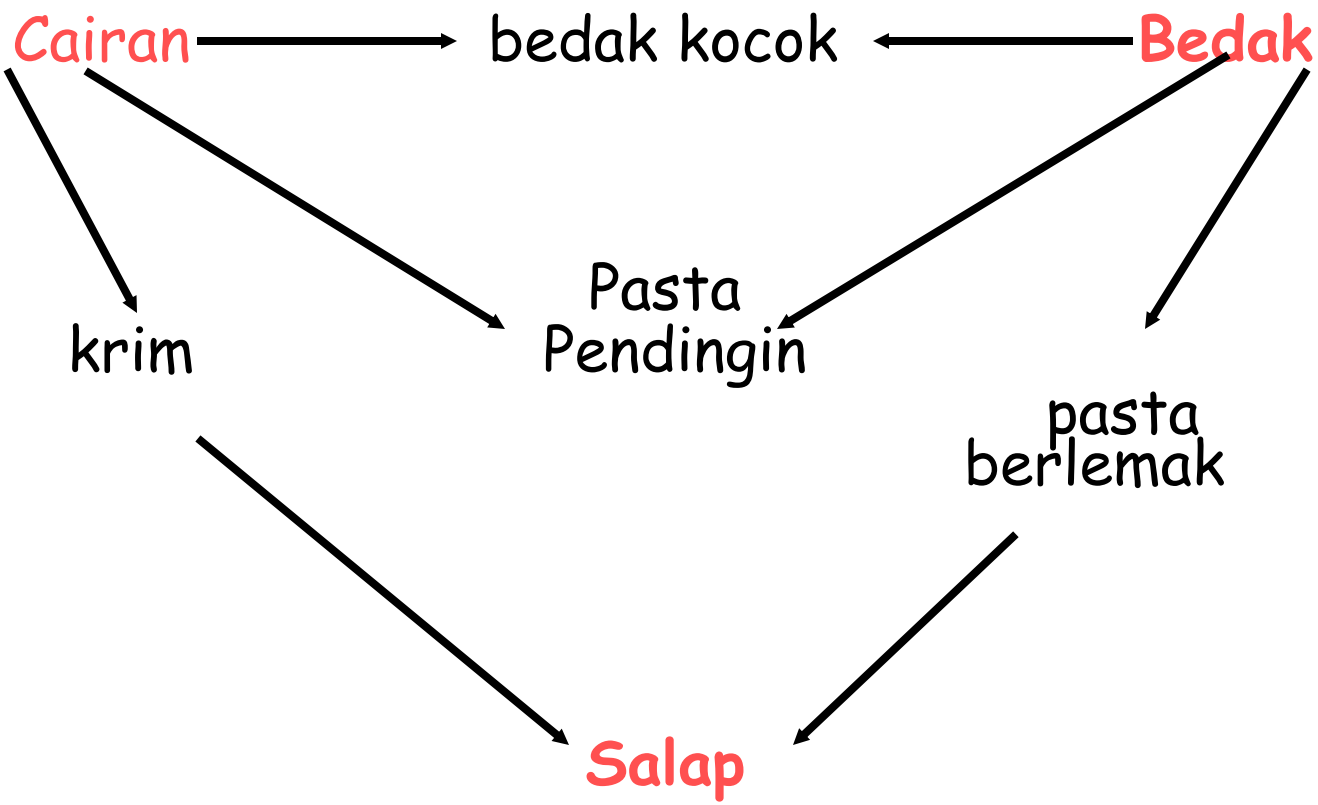
Vehikulum = zat pembawa bahan aktif

Guna Vehikulum

1. Membawa bahan aktif obat
2. Mempertinggi penetrasi obat ke kulit
3. Tidak menghambat absorbsi obat
4. Efek non spesifik :

- pendingin
- emolien
- proteksi
- oklusif

VEHIKULUM


Cairan
bedak kocok
Bedak
krim
Pasta
Pendingin
pasta
berlemak
Salap

CAIRAN

Bahan pelarut :

- Alkohol, eter, kloroform → TINGTUR
- Air ~ aqua → SOLUTIO

Solutio :

- Mandi
- Rendam
- Kompres → terbuka
  → tertutup

Prinsip terapi cairan

1. Membersihkan kulit dari krusta, skuama, debris, mikroorganisme, sisa obat
2. Melunakkan kulit
3. Mengeringkan ⟶ bersih
4. Mencegah hidupnya bakteri
5. Mempermudah proses epitelisasi
6. Menghilangkan gejala
    - Gatal
    - Rasa terbakar
    - Mendinginkan permukaan kulit
    - Penguapan dan absorbsi

Kompres Terbuka

Dasar : penguapan cairan kompres

→ absorbsi eksudat/ pus → kulit kering

Indikasi :

- Dermatosis madidans
- Erisipelas
- Ulkus berisi pus + krusta

CARA :

Kain kasa

- Non iritasi, absorben, tidak perlu steril
- 3 lapis
- Celup ke dalam air kompres → peras balutkan pada kulit (tdk perlu ketat)
- Lakukan 3x 15' -30' / hari

Cairan Kompres

- Jangan terlalu >>
- Tidak menetes
- Jangan terjadi maserasi

!!! Kapas tidak boleh digunakan

ok  penguapan

Kompres tertutup

~ impermeable

Dasar : terjadi vasodilatasi
penguapan (-)

Indikasi : untuk kelainan yang dalam

- Selulitis
- LGV

Cara : -pembalut tebal
-tutup dengan bahan impermeable
→ plastik

BEDAK

TDD : talcum venetum
+ oxydum zinzicum (seng oksida)

Efek bedak

- Mendinginkan
- Antipruritus ⟶ lemah
- Antiinflamasi ⟶ ringan
- Mengurangi gesekan pd kulit yang berlipat
- Proteksi mekanis / penutup

BEDAK

INDIKASI

1. Dermatosis kering dan superfisial
2. Mempertahankan bula / vesikel agar tidak pecah. seperti pd varisela & H. zoster

KONTRA INDIKASI

dermatitis dengan infeksi sekunder

SALAP

- Bahan berlemak ~ spt lemak
- Suhu kamar = mentega
- Bahan dasar : -vaselin
  -lanolin / minyak

Indikasi

1. Dermatosis kering dan kronik
2. Dermatosis tebal : likenifikasi, hiperkeratosis
3. Dermatosis berskuama tebal / berlapis

SALAP

Kontra indikasi

- Radang akut ⟶ eksudatif
- Daerah berambut
- Daerah lipatan

PASTA

- Campuran bedak + salap
- Sudah jarang digunakan
- Tidak dipakai pada :
  - Daerah berambut
  - Daerah lipatan
  - Kelainan kulit eksudatif

Pasta pendingin = LINIMEN

⟶ campuran salap, cairan & bedak

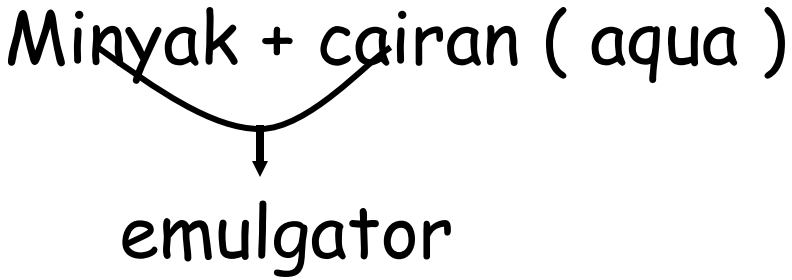
GEL

- Sediaan hidroklorid / hidrofilik
- Suspensi dr bahan organik
- Bahan-bahan
  - karbomer
  - metil selulosa
  - tragakan

+ dengan air
perbandingan ttt

GEL

KRIM



Krim ada 2 macam :

1. Cold Cream (W/O)
   - Oil >>> - daya emolien >>>
2. Vanishing Cream (O/W)
   - Water >>> - efek pendinginan >>>

Indikasi Krim

- Kelainan agak eksudatif
- Kering → superfisialis

Kelebihan krim dibandingkan salap :

- Nyaman
- Daerah lipatan
- Kulit berambut

} dapat digunakan

BEDAK KOCOK

= LOTIO

- Campuran bedak + air dan gliserin
- Pemakaian : harus dikocok dulu
- Gliserin : bahan pelekat
- Supaya tidak kental & tidak cepat kering :
  - jumlah zat padat max 40 %
  - gliserin 10 – 15 %

BEDAK KOCOK

INDIKASI

- Dermatosis yg kering, superfisial, agak luas
- Miliaria
- Keadaan sub akut

KONTRA INDIKASI

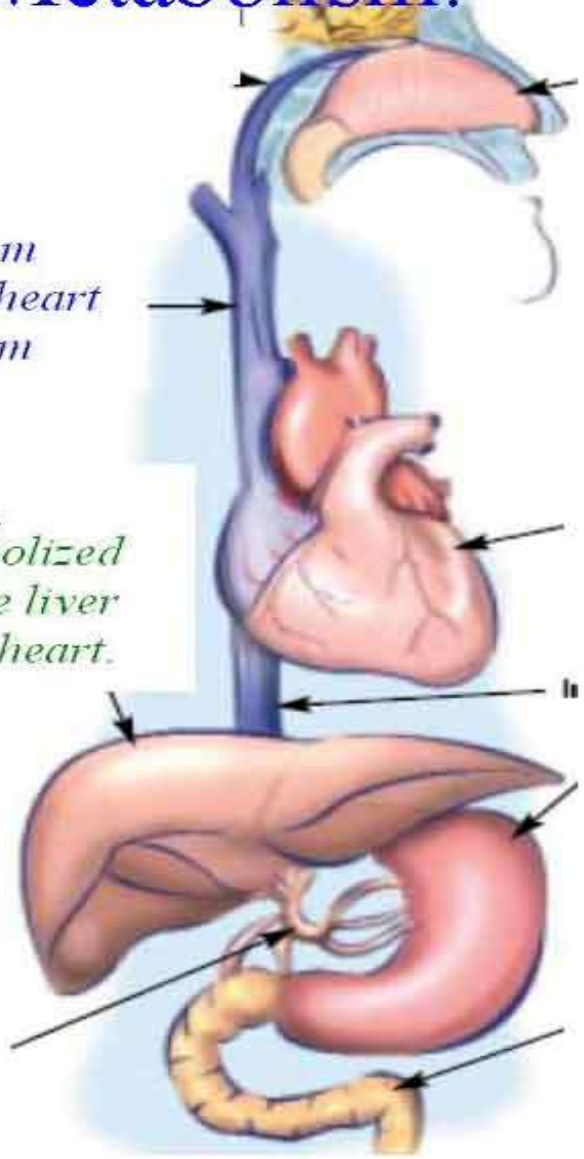
- Dermatitis madidans
- Daerah berambut

INTRANASAL DELIVERY DRUG

INTRODUCTION

- Administration of drug through nasal route is referred as Nasal drug delivery system.
- Nasal route is an alternative to invasive administrations and provides a direct access to the systemic circulation.
- Intranasal Medication administration offers a truly "Needleless " solution to drug delivery.
- In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration

First Pass Metabolism:



Nasal: *Drug absorbs directly into the veins*

Venous system: *transports blood from nose directly to the heart – no liver metabolism*

Heart: *pumps blood out to entire body – no delay*

Liver: *90% of oral medication is metabolized and destroyed by the liver before it gets to the heart.*

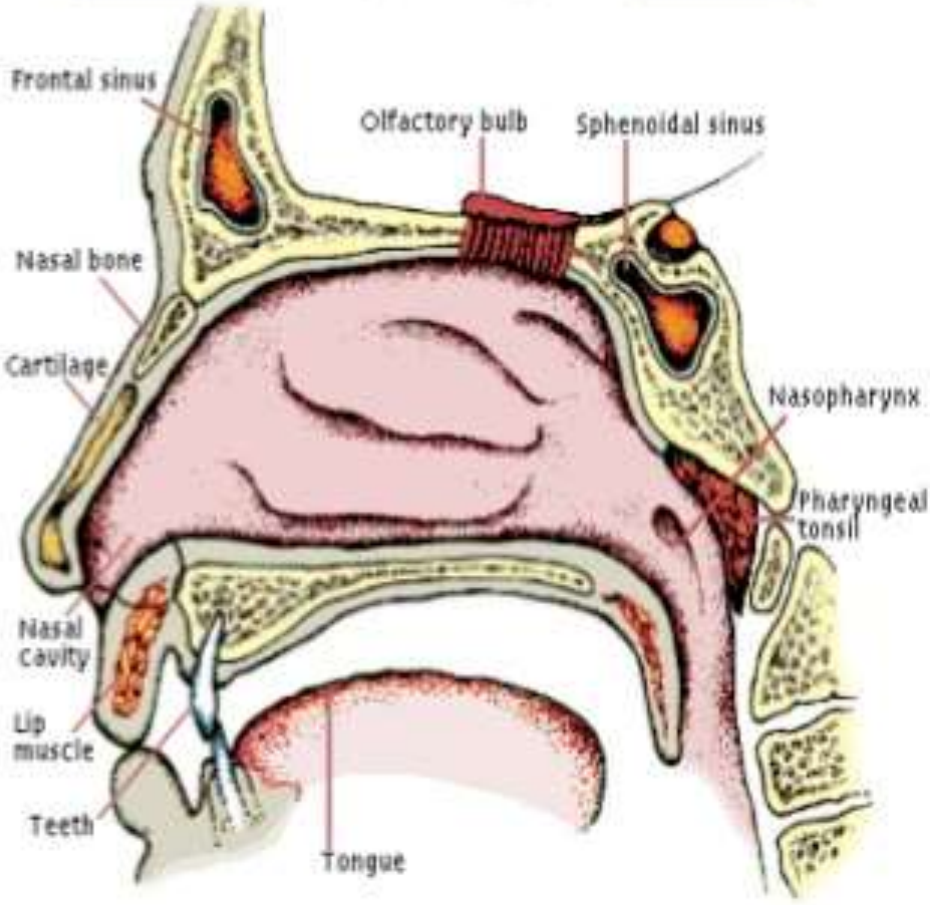
Portal circulation: *All blood from the intestines is taken to the liver for detoxification.*

Oral medications: *Sit in the stomach for 30-45 minutes*

NASAL DRUG DELIVERY SYSTEM

INTRODUCTION

- Anatomy of nose:-
- The nasal cavity consists of passage of a depth of approximately 12-14cm.
- The nasal passage runs from nasal vestibule to nasopharynx.



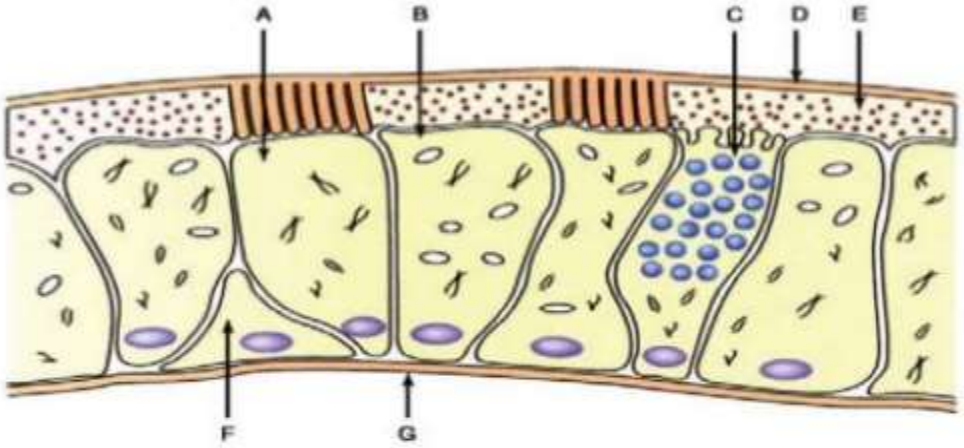


Fig. 2. Cell types of the nasal epithelium showing ciliated cell (A) Non-ciliated cell (B) Goblet cells (C) Gel mucus layer (D) Sol layer (E) Basal Cell (F) and Basement membrane(G).

12

- The lining is ciliated, highly vascular and rich in mucus gland.
- Nasal secretions are secreted by goblet cells, nasal glands and transudate from plasma.
- It contains sodium, potassium, calcium, albumin, enzymes like leucine,CYP_{450},Transaminase,etc.
- The pH of nasal secretion is 5.5-6.5 in adults and 5.0-6.7 in infants.

ANATOMY OF NASAL CAVITY

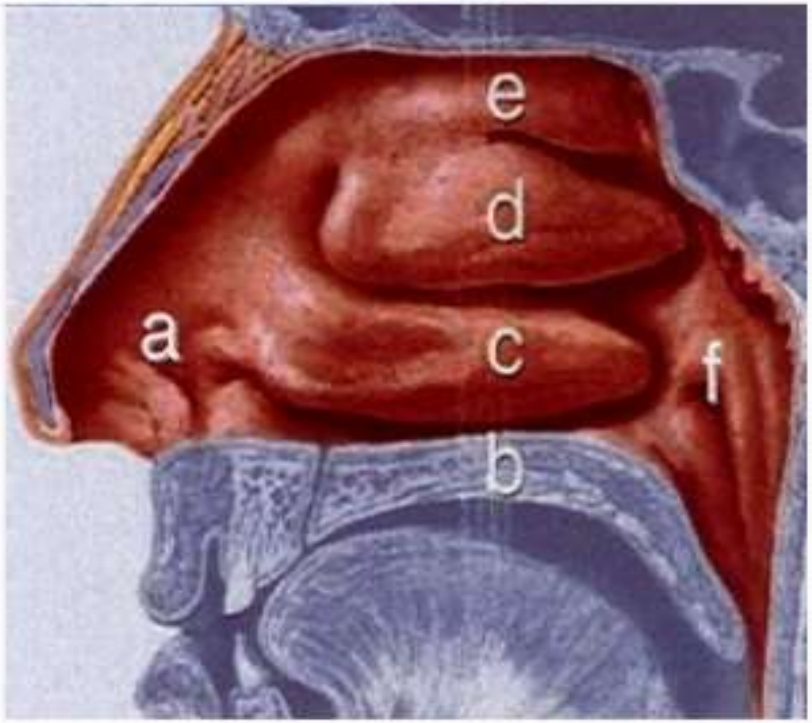
It is divided in to two halves by nasal septum.It contains 3 regions

a)Nasal vestibule

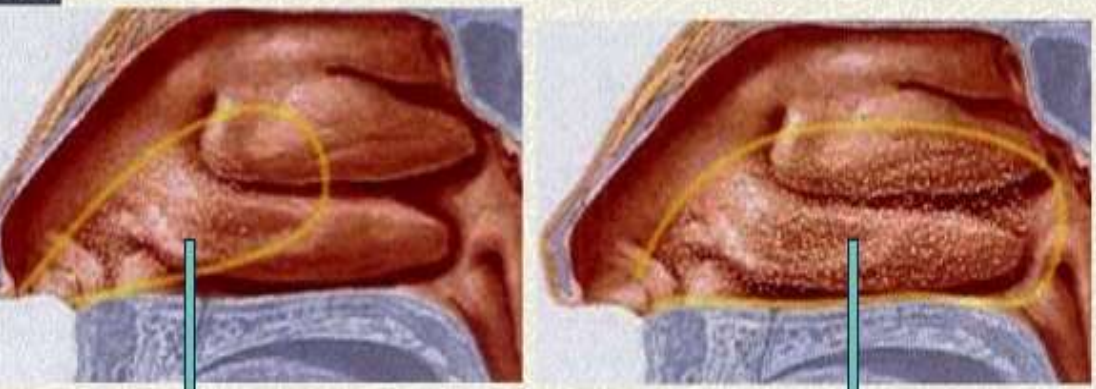
b)Olfactory region

c)Respiratory region

Nasal cavity is covered with mucous membrane which contains goblet cells and secrets mucous



a – nasal vestibule
b – palate
c – inferior turbinate
f – nasopharynx
d – middle turbinate
e – superior turbinate



Site of drug spray & absorption

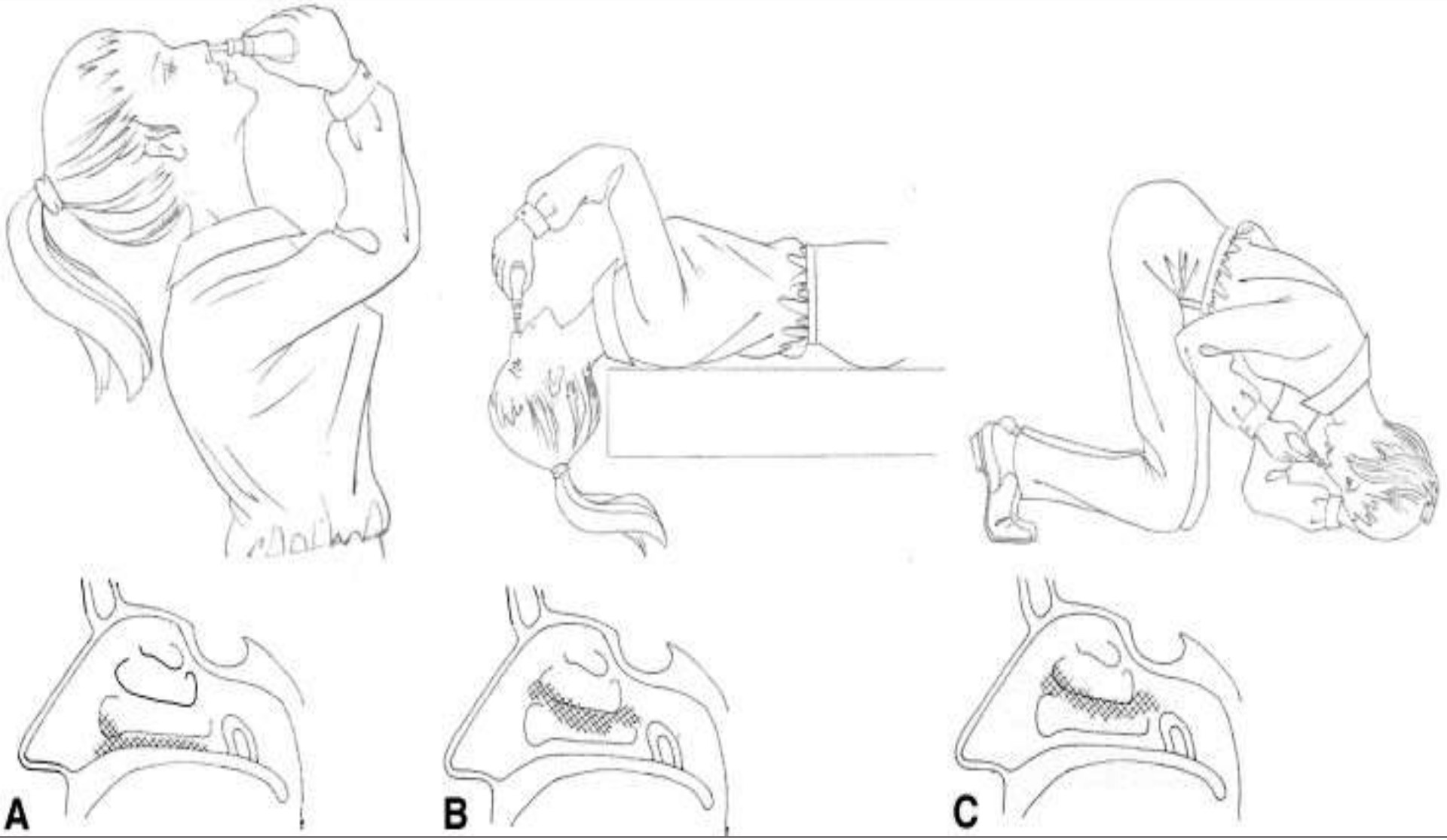
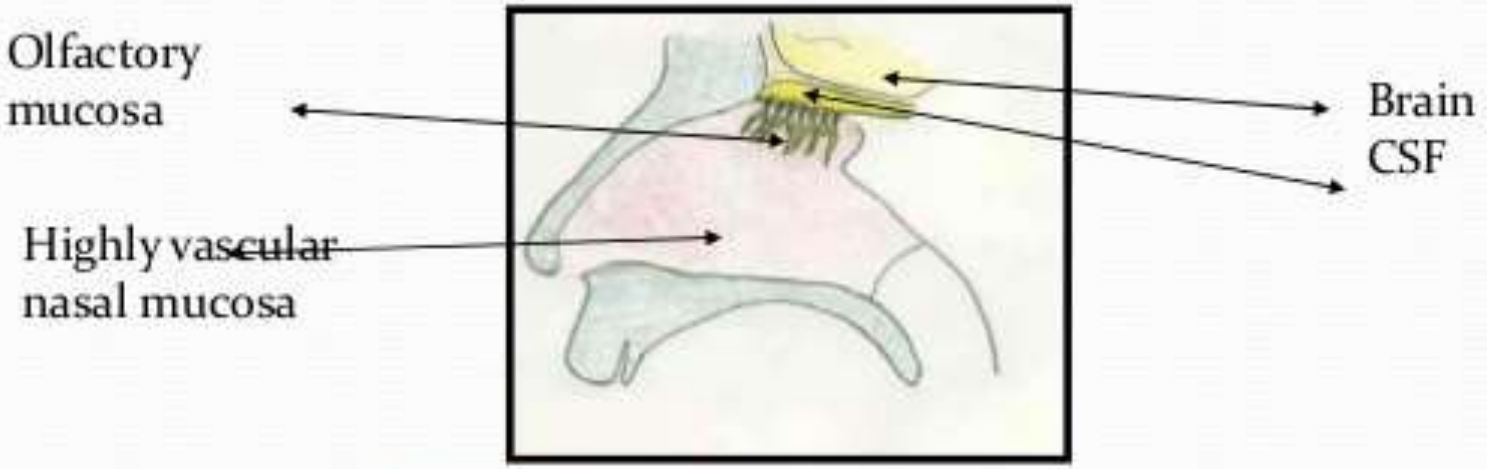


Fig 2. Distribution of blue dye (indicated by crosshatching) in the nose after instillation of topical nose drops: (*A*) head-tipped-back position, (*B*) Mygind's position, and (*C*) praying-to-Mecca position. Note distribution of the spray in the inferior portion of the nose in the head-tipped-back position (*A*). (Intranasal diagrams adapted from Kubba et al, 2000.)

NOSE BRAIN PATHWAY

- The olfactory mucosa (smelling area in nose) is in direct contact with the brain and CSF.
- Medications absorbed across the olfactory mucosa directly enter the brain.
- This area is termed the nose brain pathway and offers a rapid, direct route for drug delivery to the brain.



ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

- 1. A **non invasive** route.
- 2. Hepatic first – pass metabolism is **absent.**
- 3. **Rapid** drug absorption.
- 4. **Quick onset** of action.
- 5. The bioavailability of larger drug molecules can be improved by means of **absorption enhancer** or other approach.
- 6. **Better nasal bioavailability** for smaller drug molecules.
- 7. Drugs which can not be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
- 8. **Convenient route** when compared with parenteral route for long term therapy.

LIMITATIONS

1. The absorption enhancers used to improve nasal drug delivery system may have **histological toxicity** which is not yet clearly established
2. Absorption **surface area is less** when compared to GIT.
3. Once the drug administered **can not be removed**.
4. **Nasal irritation.**
5. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa

MECHANISM OF DRUG ABSORPTION

Paracellular transport

- Aqueous route of transport.
- Slow and passive.

Transcellular transport

- Transport through lipoidal membrane
- Active transport via carrier mediated means.

MECHANISM OF DRUG ABSORPTION

- The first step in the absorption of drug from the nasal cavity is passage through the mucus . Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross.
- Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion.
- Structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, température, etc.)subsequent to a drug's passage through the mucus.
- There are several mechanisms for absorption through the mucosa.These include transcellular or simple diffusion across the membrane, paracellular transport *via movement between* cell and transcytosis by vesicle carriers .
- Drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity.

Following mechanisms have been proposed :

1. The first mechanism involves an aqueous route of transport which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons .

2. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route *via* carrier-mediated means or transport through the openingof tight junctions.

FACTORS AFFECTING DRUG ABSORPTION

- Drug concentration
- pH of the absorption site
- Size of the drug particle
- Relative lipid solubility
- Mucosal contact time
- Molecular weight of the drug

FACTORS INFLUENCING NASAL DRUG ABSORPTION

- **Factors Related to Drug**
- ***a) Lipophilicity***
- On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa because of high lipophilicity though it has some hydrophilic character.eg: alprenolol and propranolol.

- ***b) Chemical Form***
- ***Its an important factor for absorption.***
- Conversion of the drug into a salt or ester form can alter its absorption. eg: In-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

c)Polymorphism

- Polymorphism is known to affect the dissolution rate and solubility of drugs and as well as their absorption through biological membranes.
- It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders or suspensions .

d) Molecular Weight

- In the case of lipophilic compounds, a direct relationship exists between the Molecular Weight and drug permeation where as water soluble compounds depict an inverse relationship.
- The permeation of drugs less than 300Da is not significantly influenced by the physicochemical properties of the drug, which will mostly permeate through aqueous channels of the membrane. By contrast, the rate of permeation is highly sensitive to molecular size for compounds with MW = >300 Da.

- ***e) Partition Coefficient and pKa***
- As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same holds true in the case of nasal absorption.
- Quantitative relationship between the physicochemical properties of drugs and their nasal absorption, the results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant .
- The nasal absorption of weak electrolytes such as salicylic acid and amino-pyrine was found to be highly dependent on their degree of ionization.
- Although for amino-pyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile.
- Substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, eg:salicylic Acid pathways.

- ***f) Solubility & Dissolution Rate***
- Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions.
- The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared, no absorption takes place.

B) Factors Related to Formulation

1) Physicochemical Properties of the Formulation

a) pH and Mucosal Irritancy

- The pH of the formulation, as well as that of nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 . In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.

b) Osmolarity

- *Because of the effect of osmolarity on the absorption* isotonic solutions are usually preferred for administration for shrinkage of the nasal epithelial mucosa.
- This results in increased permeation of the compound resulting from structural changes

- ***c) Viscosity***
- A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa there by increasing the time for permeation.
- At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

FORMULATION

- Drugs
- Viscosifying agents
- Solubilizers
- surfactants
- Bioadhesive polymers
- Preservatives
- Antioxidants

DRUGS

- Drugs commonly used are
- β2-adrenergic agonist: terbutaline sulphate.
- Corticosteroids : budesonide.
- Anti cholinergic: ipratropium bromide .
- Mast cell stabilizer : sodium chromogylate.

APPLICATIONS

- Delivery of non-peptide pharmaceuticals
- Delivery of peptide-based pharmaceuticals
- Delivery of diagnostic drugs
- Cns delivery through nasal route
- Nasal vaccination

1.Delivery of non-peptide pharmaceuticals:

- ✓ Drugs with extensive pre-systemic metabolism, such as
  - progesterone
  - estradiol
  - propranolol
  - nitroglycerin
  - sodium chromoglyate

can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%

2.Delivery of peptide-based pharmaceuticals:

Peptides & proteins - low oral bioavailability because of their physico-chemical instability and susceptibility to hepato gastrointestinal first-pass elimination

Eg. Insulin, Calcitonin, Pituitary hormones etc.

Nasal route is proving to be the best route for such biotechnological products

3. Delivery of diagnostic drugs

Diagnostic agents such as

- Phenolsulfonphthalein – kidney function
- Secretin – pancreatic disorders
- Pentagastrin – secretory function of gastric acid

4.CNS delivery through nasal route :

- The delivery of drugs to the CNS from the nasal route may occur via olfactory neuroepithelium
- Drug delivery through nasal route into CNS has been reported for

i. Alzheimer's disease
ii. brain tumours
iii. epilepsy
iv. pain and sleep disorders.

5.Systemic delivery:

- Fast and extended drug absorption
- Ex.- analgesics (morphine),

i. cardiovascular drugs(propranolol)
ii. hormones (levonorgestrel, progesterone)
iii. antiviral drugs

- Marketed formulation- zolmitriptan and sumatriptan

6.Nasal vaccines

- Nasal mucosa is the first site of contact with inhaled antigens and therefore, its use for vaccination, especially against respiratory infections, has been extensively evaluated.
- Ex. Human efficacy of intranasal vaccines include those against influenza A and B virus, proteosoma-influenza, adenovirus-vectored influenza, group B meningococcal native, attenuated respiratory syncytial virus and parainfluenza 3 virus.

VISCOSIFYING AGENTS

These agents increase the viscosity of the solution prolonging the therapeutic activity of preparation. e.g.: hydroxypropyl cellulose.

SOLUBILIZERS

Aqueous solubility of drug always a limitation for nasal drug delivery. e.g.: glycol, alcohol, labrasol, transcutol.

In such cases surfactants or cyclodextrines (HP- β -cyclodextrine) are used , these serve as a biocompatible solubilizer & stabilizer in combination with lipophilic absorption enhancers.

SURFACTANTS

Modify the permeability of nasal mucosa & facilitate the nasal absorption of drugs. E.g. SLS, Poly acrylic acid, sod.glycocholate.

BIOADHESIVE POLYMERS

Increases the residence time of drug in nasal cavity and a higher local drug concentration in the mucus lining on the nasal mucosal surface E.g.: Methylcellulose, Carboxymethylcellulose Hydroxyl propyl cellulose

PRESERVATIVES

These are used to prevent the growth of micro organisms. e.g.: parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA etc.

ANTIOXIDANTS

These are used to prevent drug oxidation. E.g.: sodium meta bisulphite , sodium bisulfite, butylated hydroxy toluene& tocopherol etc.

POLYMERS FOR NASAL DDS:

Mucoadhesive polymer	Drug	Dosage form	Reference
CMC	Apomorphine	Powder	Ugwoke MI *et al.*[7]
MCC	Ketorolac acid	Spray	Quadir M *et al.*[44]
MCC/HPC	Leapralide	Powder	Suzuki Y *et al.*[28]
HPC	Dopamine	Liquid	Ikeda K *et al.*[38]
HPC	Metaclopramide	Gel	Zaki NM *et al.*[32]

DOSAGE FORMS

- Liquid drop
- Liquid spray/nebulizers
- Aerosol
- Suspension spray/nebulizers
- Gel
- Sustained release

Nasal drops

✓ Most simple and convenient systems developed for nasal delivery.

✓ It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

✓ Disadvantage-lack of the dose precision .

Nasal sprays

✓Both solution and suspension formulations can be formulated into nasal sprays.

Deliver an exact dose from 25 to 200 µm.

Nasal Gels

✓Nasal gels are high-viscosity thickened solutions or suspensions.

Advantages of a nasal gel

- Reduction of post-nasal drip due to high viscosity,
- Reduction of taste impact due to reduced swallowing,
- Reduction of anterior leakage of the formulation,
- Reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

JNTUH,CPS,13031S0304

Mucosal Atomization Device (MAD)

- ✓ Device designed to allow emergency personnel to delivery nasal medications as an atomized spray.
- ✓ Broad 30-micron spray ensure excellent mucosal coverage.

Rabbit Model:

- The rabbit is anaesthetized by an intramuscular injection of a combination of ketamine and xylazine. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad. The blood samples are collected by an catheter in the marginal ear vein or artery.

CONCLUSION

- An accessible alternative route for drug administration.
- Provides **future potential** for several drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy.
- Drugs can be **directly target to the brain** in order to attain a good therapeutic effect in CNS with reduced systemic side effects.
- Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery system.

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OCULAR DRUG DELIVERY

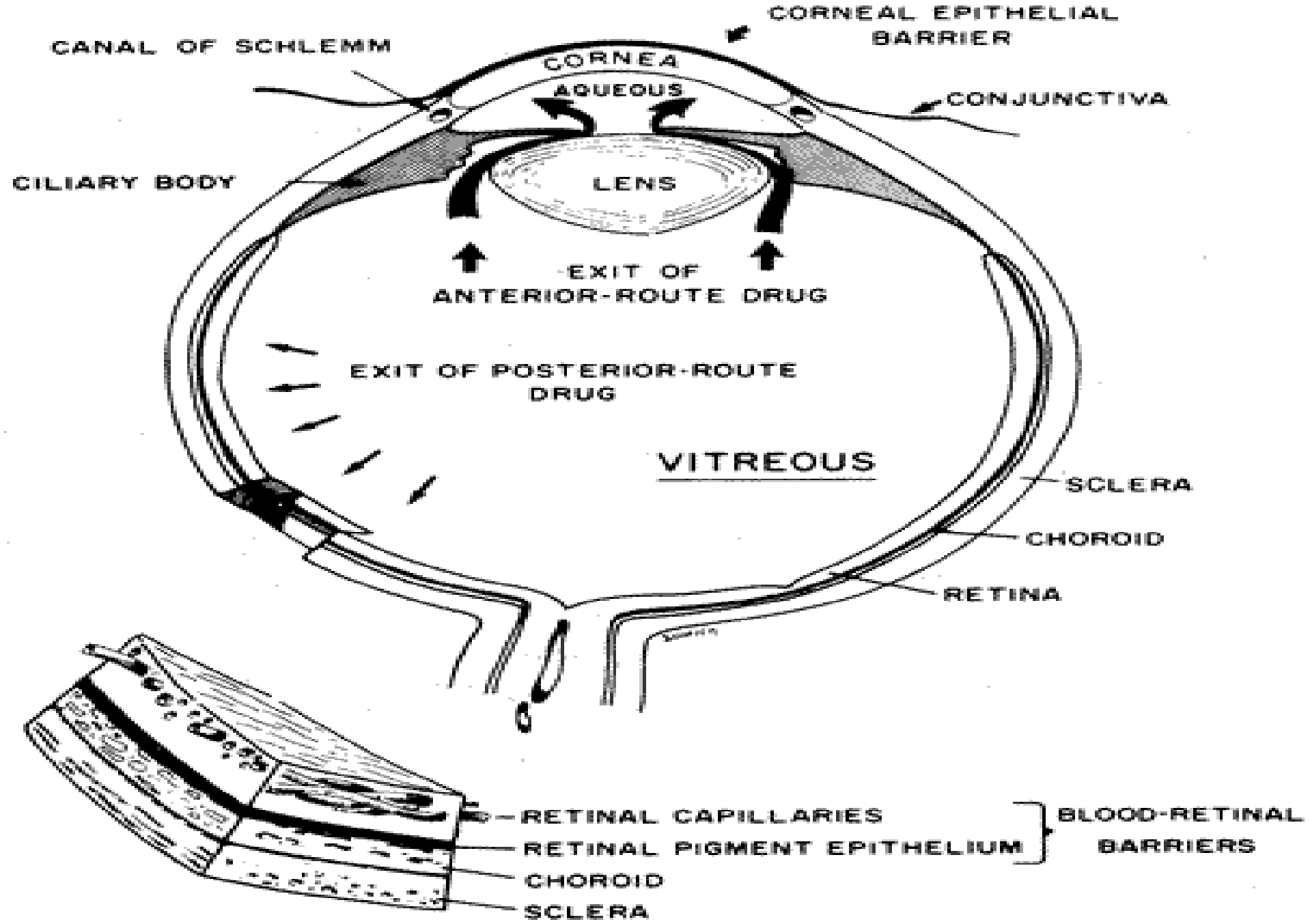
INTRODUCTION

Ocular administration of drug is primarily associated with the need to treat ophthalmic diseases.

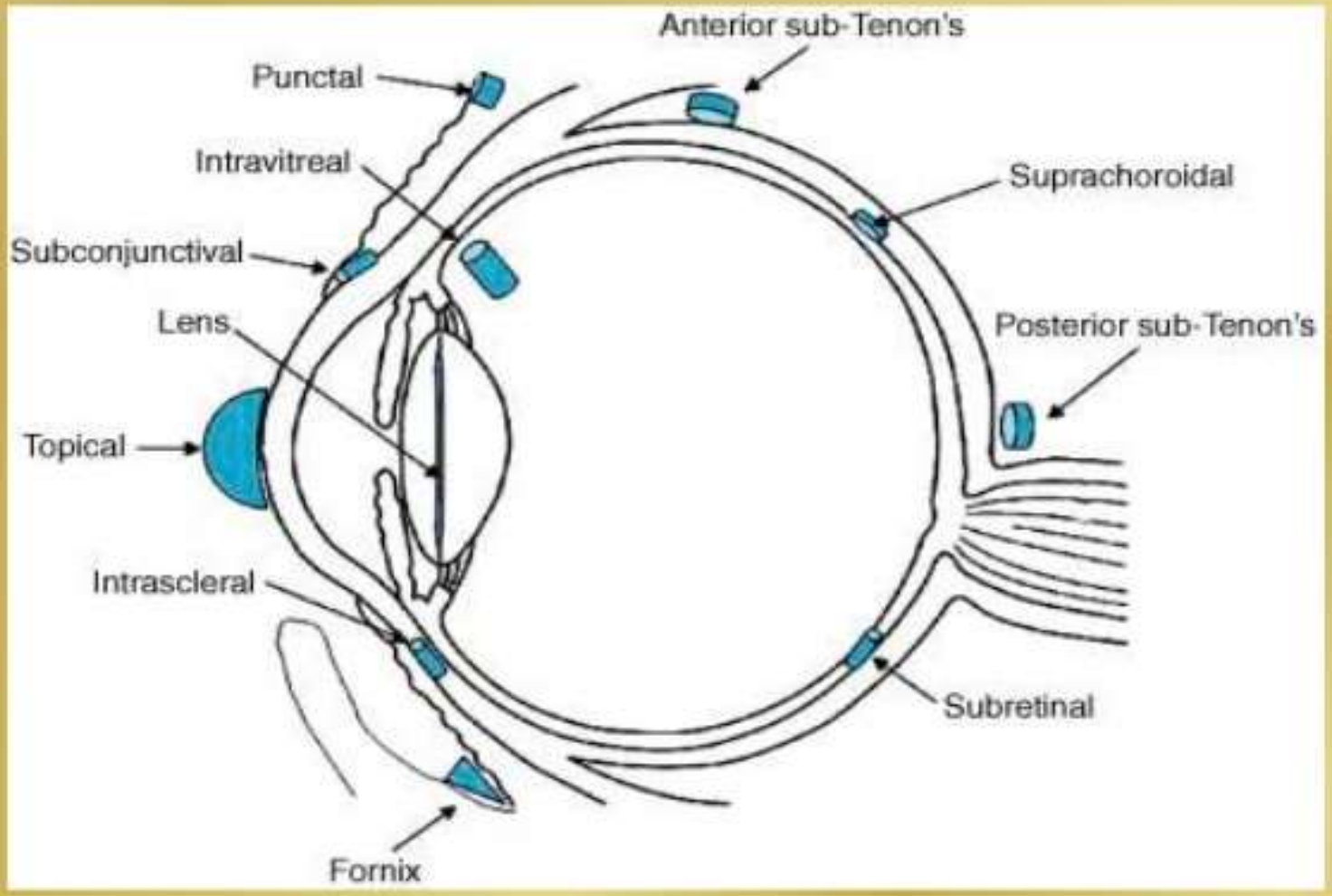
Major classes of drugs used are :

Miotics
Mydriatics
anti-inflammatories
Anti-infectives
Surgical adjuvents
Diagnostics

These drugs are meant for local therapy and not for systemic action.


CANAL OF SCHLEMM
CORNEAL EPITHELIAL BARRIER
CORNEA
AQUEOUS
CONJUNCTIVA
CILIARY BODY
LENS
EXIT OF ANTERIOR-ROUTE DRUG
EXIT OF POSTERIOR-ROUTE DRUG
VITREOUS
SCLERA
CHOROID
RETINA
RETINAL CAPILLARIES
RETINAL PIGMENT EPITHELIUM
CHOROID
SCLERA
BLOOD-RETINAL BARRIERS

ROUTES OF DRUG DELIVERY IN EYE



Fluid systems in eye-

1. Aqueous humor:

- ✓ Secreted from blood through epithelium of the ciliary body.
- ✓ Secreted in posterior chamber and transported to anterior chamber.

2. Vitreous humor:

- ✓ Secreted from blood through epithelium of the ciliary body.
- ✓ Diffuse through the vitreous body.

Lacrimal glands:

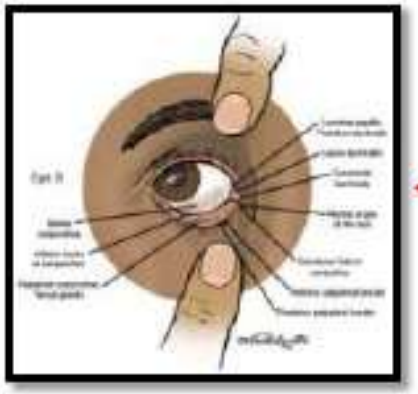
- ✓ Secrete tears & wash foreign bodies.
- ✓ Moistens the cornea from drying out.

Opthalmic products are the sterile products meant to instillation in to the eye in the space between **eye lid and the eye ball**.

These products must be sterile and are prepared under the same condition and by the same methods as other Parenteral preparations.

opthalmic products includes:

1) **Eye drops**
2) **Eye lotion**
3) **Eye ointment**
4) **Eye suspension**
5) **Contact lens solution**



EYE LID

EYE BALL

REQUIREMENTS

Opthalmic preparations should possess the following properties:

1) **Foreign particles**
2) **Viscosity**
3) **Tonicity**
4) **pH of preparations**
5) **Sterility**
6) **Surface activity**

1) **Foreign particles:**

All the opthalmic products should be clear and free from foreign particles, fibers and filaments.

Opthalmic solutions should be clarified very carefully by passing through bacteria proof filters such as membrane filters, sintered glass filters.

The particle size of the eye suspension should be in an ultrafine state of subdivision to minimize irritation.

A separate filter should be used for different opthalmic products in order to avoid the contamination.

2) Viscosity:

in order to prolong the contact time of the drug in the eye, various thickening agents are added in the opthalmic preparations.

Polyvinyl alcohol (1-4%), polyethylene glycol, methyl cellulose, carboxy methyl cellulose are some of the commonly used thickening agents. These agents improve the viscosity of the preparation.

An ideal thickening agent should possess the following properties:-

1) it should be easy to filter.
2) It should be easy to sterilize.
3) It should be compatible with other ingredients.
4) It should possess requisite refractive index and clarity level.

Thickening agents are not included in the formulation of eye drops and eye lotions which are required to be used during or after surgery due to some possible adverse effects on the interior of the eye.

3) Tonicity:

Opthalmic products should be isotonic with lachrymal secretions to avoid discomfort and irritation.

It has been observed that eye can tolerate a range of tonicity from 0.5-2% NaCl. There are certain isotonic vehicles which are used to prepare opthalmic products like 1.9% boric acid, sodium acid phosphate buffer.

4) pH of the preparations:

pH plays an important role in therapeutic activity, solubility, stability and comfort to the patient.

Tears have a pH of about 7.4. eye can tolerate solution having wide range of pH provided they are not strongly buffered, since the tear will rapidly restore the normal pH value of the eye.

Alkaloid salt solutions are stable at pH 2-3 but this pH is irritant to eye.

The alkaloids get precipitated at pH above 7 and creates a number of formulation problems.

5) sterility:

Opthalmic preparations must be sterile when prepared.

Pseudomonas aeroginosa is very common gram –ve bacteria which is generally found to be present in opthalmic products. It may cause serious infections of cornea. It can cause complete loss of eye sight in 24-48 hrs.

To maintain sterility in multi dose container, containing opthalmic products, a suitable preservative is added. The preservative should be non-toxic, non-irritant and should be compatible with medicaments. The opthalmic products are generally sterilized by autoclaving, filtration through bacteria proof filters and addition of bactericides at low temperature.

6) Surface activity:

Vehicles used in opthalmic preparations must have good wetting ability to penetrate cornea and other tissues.

Certain surfactants or wetting agents added which are found suitable for opthalmic products.

It should not cause any damage to the tissue of eye.

Benzalkonium chloride, polysorbate 20, polysoabate 80, dioctyl sodium sulpho succinate etc., are some of the surfactants which are commonly used.

1)Drug

These contains drug of various categories including antiseptic, anti-inflammatory agent, mydriatric or meiotic properties.

2) Preservative

Eye drop should be sterile and should contain preservatives to avoid microbial contamination when the container is open. The preservative for opthalmic use includes Benzalkonium chloride, Chlorbutanol, Phenylmercuric acetate, Phenylmercuric nitrate etc

3) Sterilization

Eye drops are sterilized by autoclaving at 121^0C for 15 minutes or by bacteria filter to avoid thermal degradation; for example- Preservative chlorbutanaol hydrolyzes at high temperature.

4) Isotonicity

All the solutes including drug contribute to the osmotic pressure of the eye drop, therefore isotonicity of the formula should be calculated and it is adjusted with sodium chloride, for example- Sodium chloride 0.9% and boric acid 1.9% are iso-osmotic.

5) Buffer

The buffer should be added to maintain balance between comfort, solubility, stability and activity of drug. For example-, the hydrolyzed chlorbutanol forms hydrochloride acid making the drop acidic, whereas certain drug like pilocarpine hydrochloride are acidic.

On the hand certain drug such as alkaloids show precipitation at lachrymal pH. Boric acid, monobasic sodium phosphate are the common buffers for eye drop.

CLASSIFICATION OF OPHTHALMIC DOSAGE FORMS:

A) Based on Route of Administration

- **1.Topical Sol^{n}**: Multiple Dose container With Preservatives.
- **2. Intra-ocular Sol^{n}**: For Surgery, Single dose, Without preservative.
- **3.Ophthalmic Sol^{n} Injections**: Intra-ocular injection, given in eye tissues, without preservative.

B) Based on Physical Form

- **1. Aqueous Sol^{n}.**
- **2. Suspension.**
- **3. Ointments.**
- **4. Gels.**
- **5. Eye Lotions.**
- **6. Solid Inserts.**

Types of opthalmic products

Opthalmic products may be categorized into a number of groups:

1) **Liquid preparations for application to the surface of the eye such as eye drops and eye lotions.**

2) **Semi solid preparations such as eye ointments, creams and gels for application to the margin of eye lid or for introduction in to the conjuctival sac.**

3) **Solid preparations such as Ocular inserts intended to be placed in contact with the surface of the eye to produce modified release of medicament over a prolonged period.**

4) **Parenteral products for sub conjuctival or intra ocular injection.**

5) **Liquid products for irrigation of the eye during surgical procedures.**

All opthalmic products are required to be sterile and free from extraneous particulate matter. Solutions used during surgery should not contain any preservative.

Solution

✓Dilute with tear and wash away through lacrimal apparatus.

✓Usually do not interfere with vision of patient.

×To be Administered at frequent intervals.

Suspension

✓Longer contact time.

×Irritation potential due to the particle size of the drug.

Ointment

✓Longer contact time and greater storage stability.

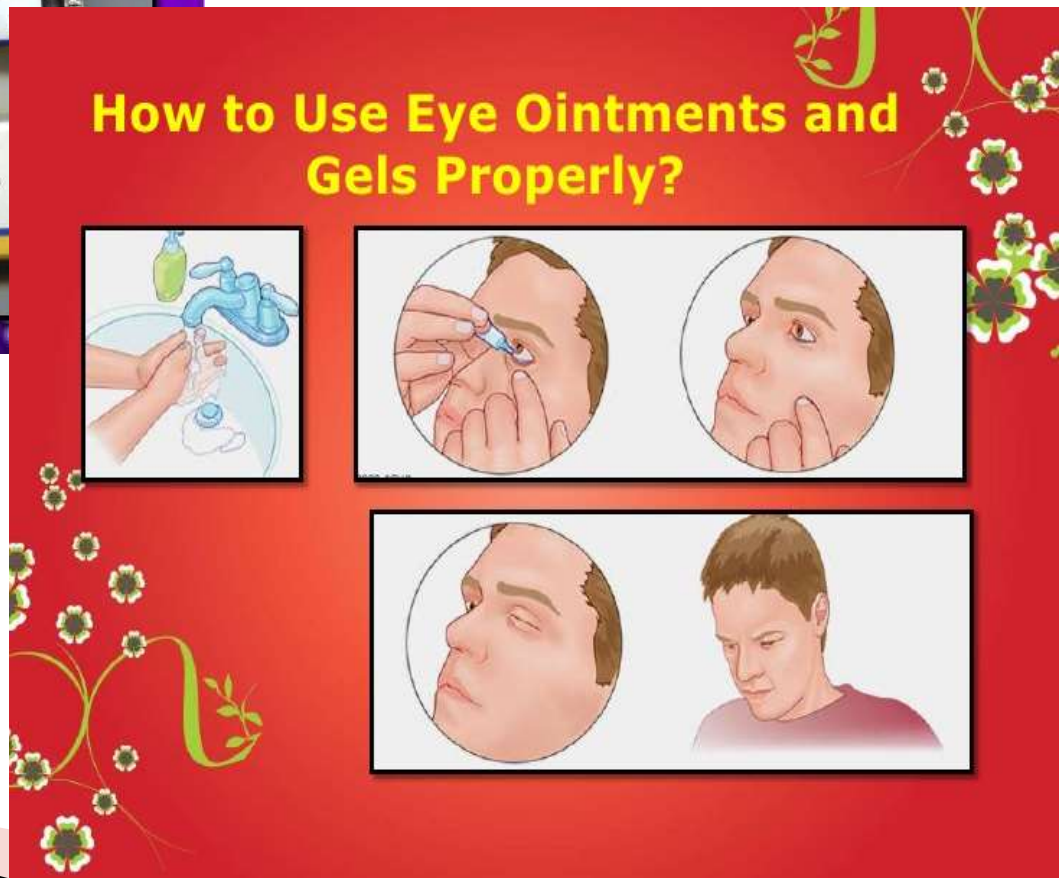
×Producing film over the eye and blurring vision.

×Interfere with the attachment of new corneal epithelial cells to their normal base.

EYE DROPS

EYE LOTION


EYE
OINTMENT
Acivir Eye Ointment
Cipla
Terramycin


How to Use Eye Ointments and
Gels Properly?

EYE SUSPENSION

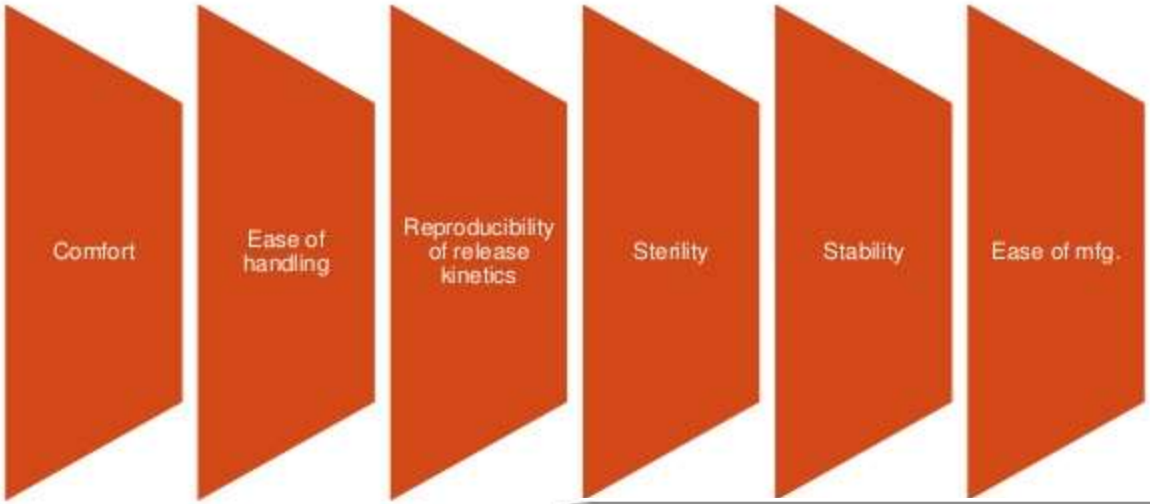
CONTACT LENSE

Ocular Control Release System: Ophthalmic Inserts

Definition:- Solid or Semisolid in nature,

- Placed in lower Fornix
- Composed of Polymeric vehicle containing drug.

Desired Criteria For Control Release Ocular Inserts.



Indication	Drug & Disease
1. Short, topical ocular half-life	Heparin for Ligneous disease
2. Small, topical ocular, therapeutic index	Pilocarpine for chronic open-angle Glaucoma
3. Systemic side effects	Timolol for Glaucoma and cyclospo for graft rejection
4. Need for combination therapy	Cromoglycate and corticosteroid fo Asthma and Allergies
5. Drug delivery over a prolonged period	Acute corneal infections, Corneal G rejection episodes
6. Long-continued low dosage for therapy or prophylaxis	Prevention of Corneal Graft Rejecti Herpetic diseases,

OCULAR CONTROL RELEASE SYSTEM:

OPHTHALMIC INSERTS

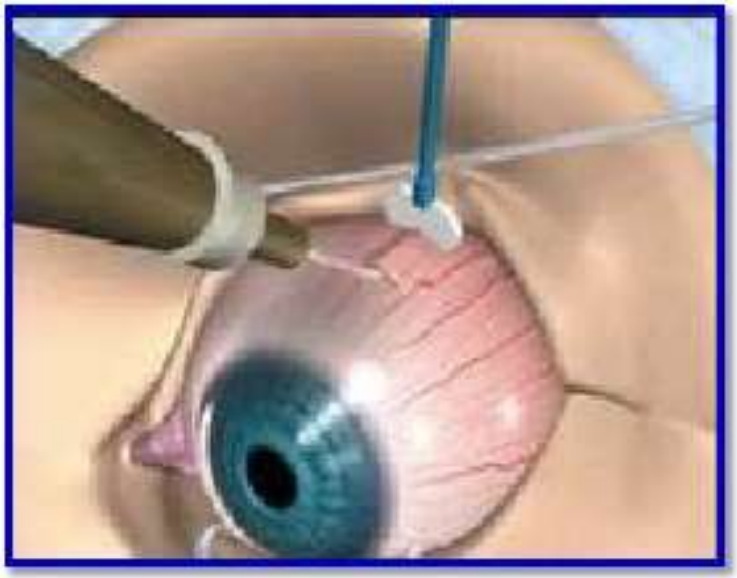
Definition:- Solid or Semisolid in nature.
- Placed in lower Fornix
- Composed of Polymeric vehicle containing drug.

Role Of Polymer In ODDS.

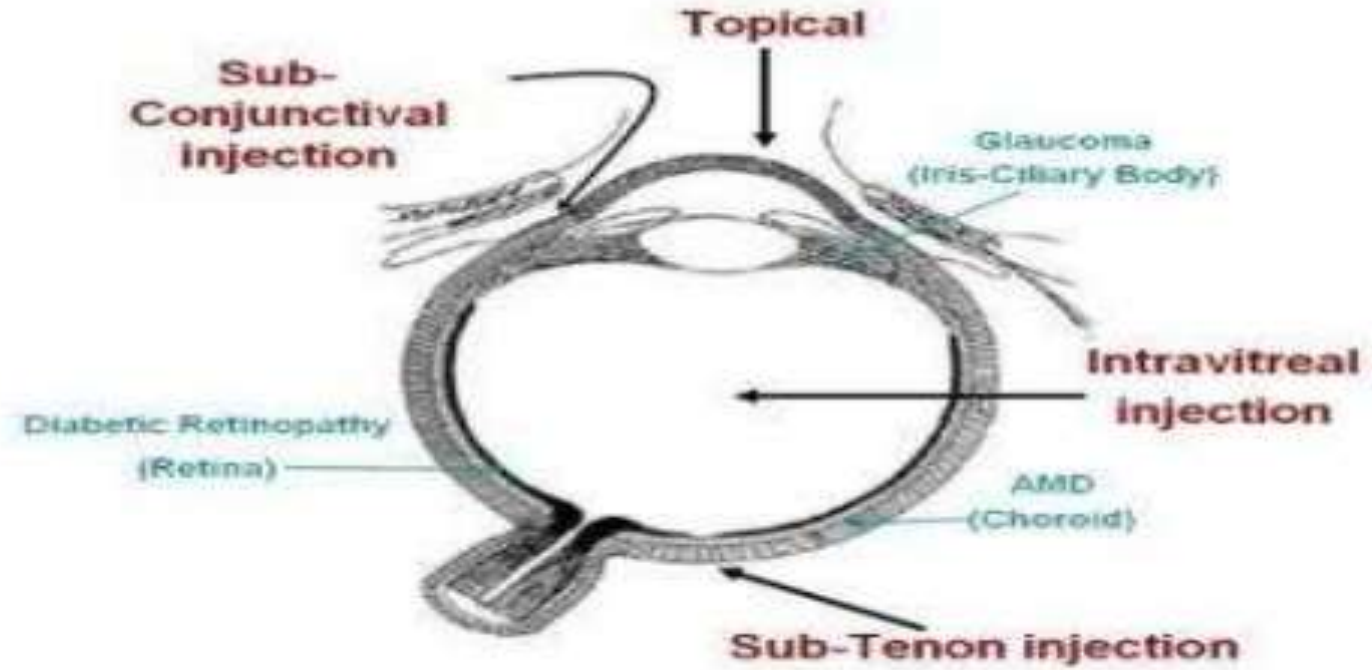
↑ Solution Viscosity : ↓ Solution Drainage.

Polymer Mucoadhesive Vehicle: Retained in the eye due to non-covalent bonding with conjuctival mucine.
Mucine is capable of picking of 40-80 times of weight of water.

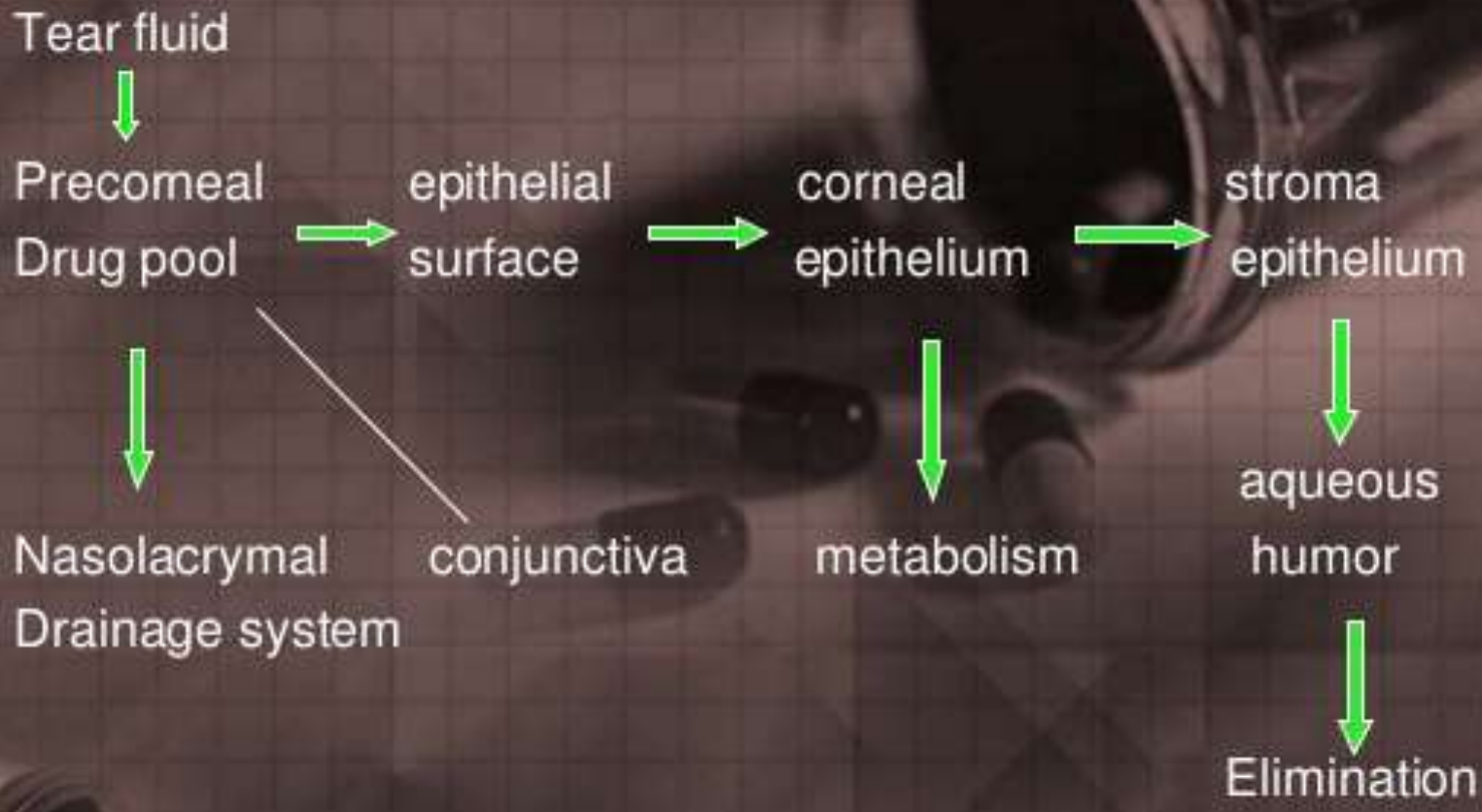
OCULAR INJECTION



Routes of Ocular Delivery



Pharmacokinetics of ocular drug administration



Mechanism of Ocular Absorption

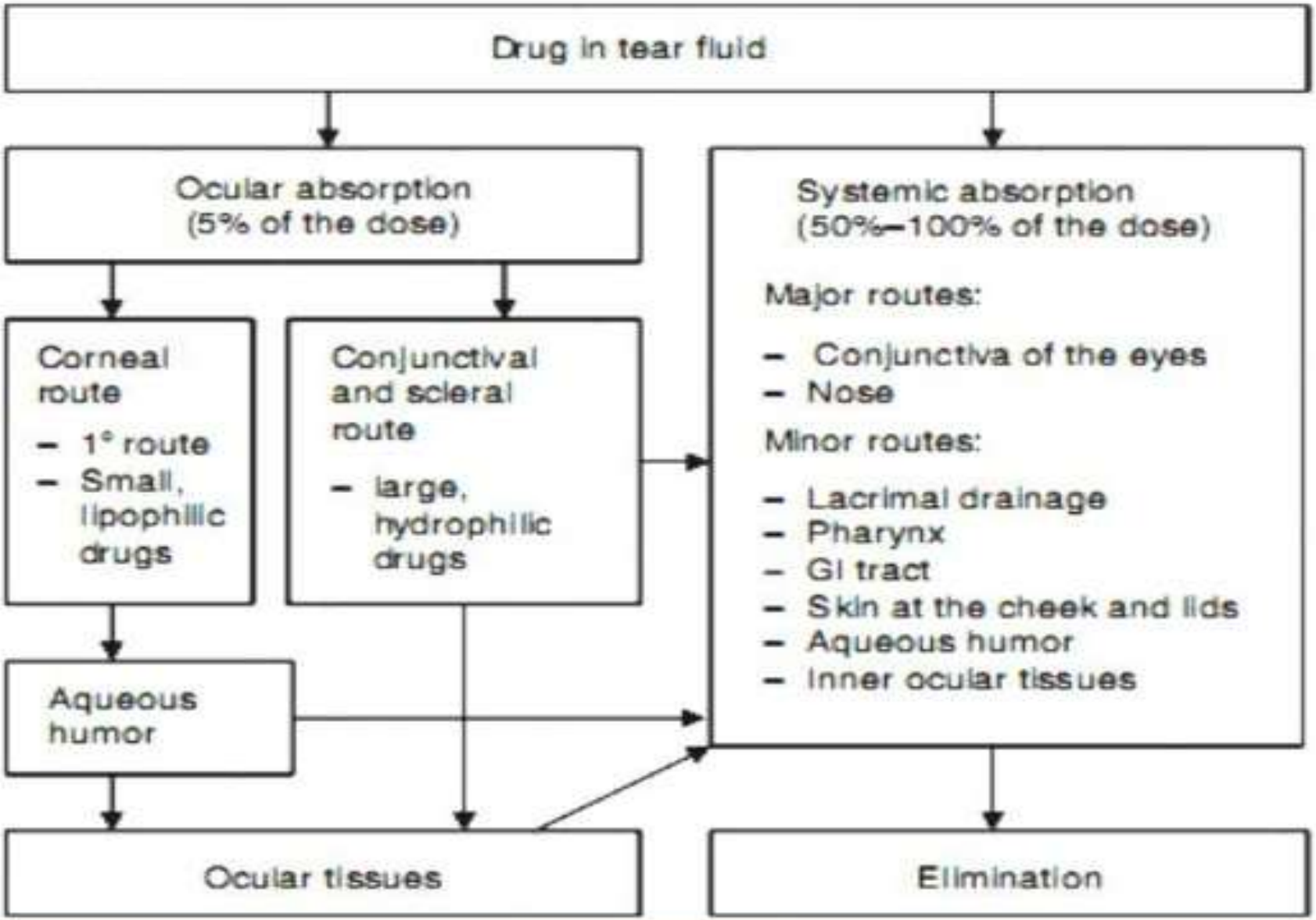
Non-Corneal Absorption

- Penetration across Sclera & Conjuctiva into Intra Ocular tissues
- Non-Productive: because penetrated drug is absorbed by general circulation

Corneal Absorption

- Outer Epithelium: rate limiting barrier, with pore size 60 å,
- Only access to small ionic & lipohilic molecules
- Trans cellular transport: transport between corneal epithelium & stroma.

GENERAL PATHWAY FOR OCULAR ABSORPTION



FACTORS AFFECTING INTRAOCULAR BIOAVAILABILITY:

1. Inflow & outflow of lacrimal fluids.
2. Efficient naso-lacrimal drainage.
3. Interaction of drug with proteins of lacrimal fluid.
4. dilution with tears.
5. Corneal barriers.
6. Active ion transport at cornea.

BARRIERS AVOIDING DRUG DELIVERY

Drug in tear fluid

Ocular absorption

Corneal route

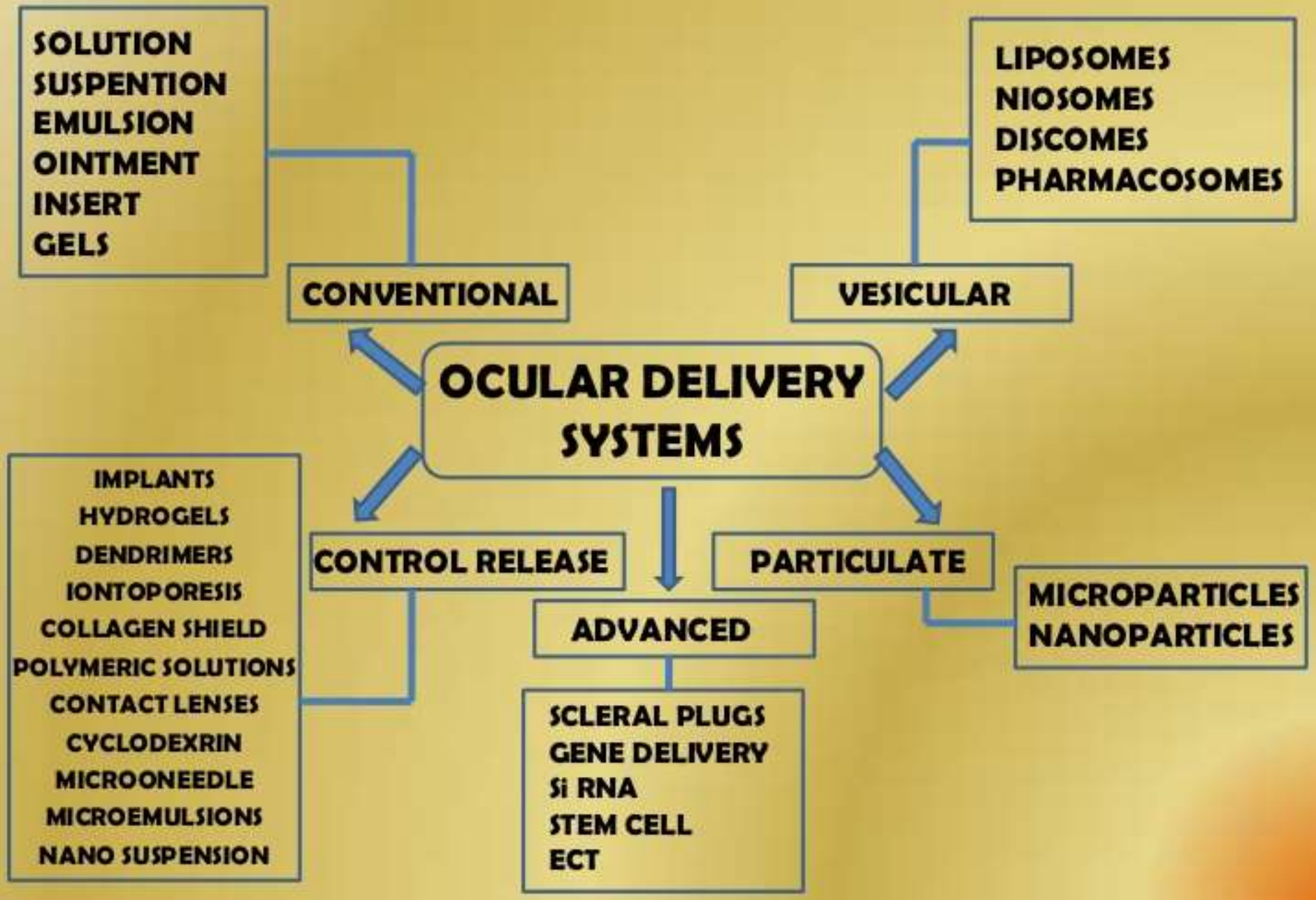
Conjunctival and scleral route

Systemic absorption
50-100% of dose
Major route- conjunctiva of eye, nose
Minor route- lacrimal drainage system, pharynx, GIT, aqueous humor

Aqueous humor

Ocular tissue

ELIMINATION


SOLUTION
SUSPENTION
EMULSION
OINTMENT
INSERT
GELS
CONVENTIONAL
LIPOSOMES
NIOSOMES
DISCOMES
PHARMACOSOMES
VESICULAR
OCULAR DELIVERY SYSTEMS
IMPLANTS
HYDROGELS
DENDRIMERS
IONTOPORESIS
COLLAGEN SHIELD
POLYMERIC SOLUTIONS
CONTACT LENSES
CYCLODEXRIN
MICROONEEDLE
MICROEMULSIONS
NANO SUSPENSION
CONTROL RELEASE
PARTICULATE
MICROPARTICLES
NANOPARTICLES
ADVANCED
SCLERAL PLUGS
GENE DELIVERY
Si RNA
STEM CELL
ECT

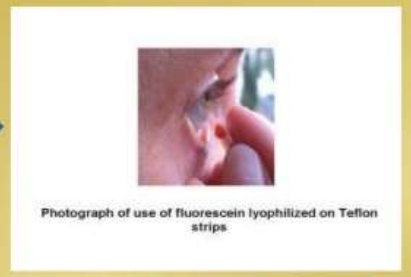
SELECTED TYPES OF OCDDS:

1. Aqueous eye drops
2. Oily eye drops

3. Eye ointments

4. Eye lotions

5. Paper strips



6. Ocuserts

7. Hydro gel contact lenses

8. Collagen shields

9. Ophthalmic rods

FORMULATION OF OCULAR DRUG DELIVERY SYSTEM:

Dosage Form	Advantages	Disadvantages
solutions	convenience	Rapid precorneal elimination, non sustained action
suspension	Patient compliance, best for drug with slow dissolution	Drug properties decide performance loss of both solutions and suspended particles
emulsion	Prolonged release of drug from vehicle	Blurred vision, patient non compliance
ointment	Flexibility in drug choice, improved drug stability	Sticking of ey… vision, poor p… compliance

RECENT FORMULATION TRENDS IN OCDDS:

1. CONVENTIONAL DELIVERY SYSTEMS:

Eye Drops:

- **Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension.**
- **Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye.**
- **Less than 5 % of the dose is absorbed after topical administration into the eye.**
- **The dose is mostly absorbed to the system… on via the conjunctival and nasal blood vessels.**

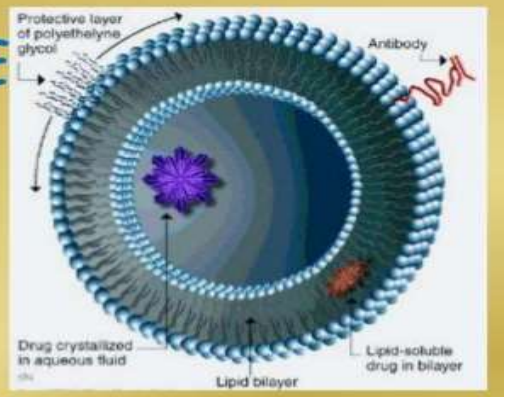
Ointment and Gels:

- **Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision & matting of eyelids can limit its use.**

Ocuserts and Lacrisert:

- **Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.**
- **Inserts are available in different varieties depending upon their composition and applications.**
- **Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca.**
- **They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.**

2) VESICULAR SYSTE



Liposomes:

➢Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.

➢ They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorptior

Niosomes and Discomes:

➢The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids.

➢ To avoid this niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs.

➢They are non toxic and do not require special handling techniques.

- Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs.
- Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

✓Discosomes are giant niosomes (about 20 um size) containing poly-24- oxy ethylene cholesteryl ether or otherwise known as Solulan 24.

- Pharmacosomes: This term is used for pure drug vesicles formed by the amphiphilic drugs.

The amphiphilic prodrug is converted to pharmacosomes on dilution with water.

TERIMA KASIH ……