Faculty of Pharmacy

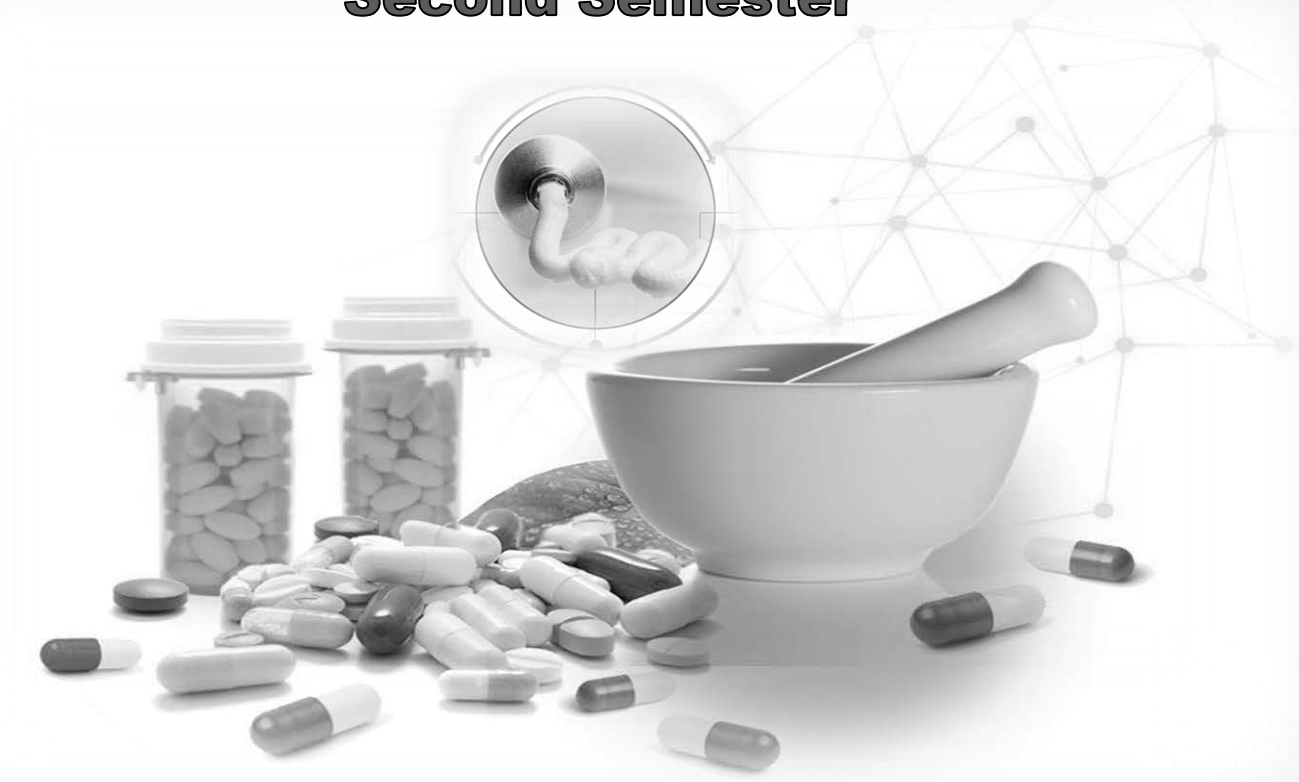
Menoufia University

Pharmaceutical Formulations

For

Second Year Pharmacy Students

Second Semester



By Staff Members Of

Pharmaceutical Technology Department

Menoufia University, Faculty of Pharmacy
Course Specifications

Pharmaceutical Formulations
Second Year, Second Semester

Professional Information
1. Overall aims of the course
Upon successful completion of this course, the students should be able to:

- Recognize the factors affecting percutaneous and rectal absorption of drugs.
- Utilize different strategies to enhance percutaneous absorption.
- Design transdermal therapeutic systems.
- Formulate ointments, creams and suppositories.
- Recognize the specifications of selected cosmetic formulations.

2. Intended learning outcomes of the course (ILOs)
a- Knowledge and understanding:
On successful completion of the course, the graduate should be able to:

- a1- Discuss the factors affecting percutaneous and rectal absorption of drugs
- a2- Recognize different methods of enhancing percutaneous absorption of drugs.
- a3- Describe the transdermal therapeutic systems.
- a4- Classify different bases used in formulation of ointments, suppositories and cosmetic formulation.
- a5- Express knowledge of methods of preparation of suppositories, ointment and cosmetic products.

b- Intellectual skills:

- b1- Select the best enhancer for a given transdermal therapeutic system.
- b2- Predict drug interaction with different bases.
- b3- Select the best topical formulation based on the disease state of the patient and the required effect.

c- Professional and practical skills:

- c1- Formulate topical formulations for local and transdermal effects.
- c2- Design rectal and cosmetic formulations.
- c3- Prepare ointments, suppositries and other topical formulations.
- c4-Assess the quality of topical, suppositories and cosmetic products.

d- General and transferable skills

- d1-Retrieve and evaluate information on pharmaceutical formulation.
- d2-Demonstrate critical thinking, problem solving and decision making abilities.
- d3-Demonstrate leadership and team working abilities.

3. Teaching and learning methods

a. Lectures
b. Practical training / laboratory
c. Seminar / Workshop
d. Class Activity

Topical formulations

Aims of the course

- Recognize the factors affecting percutaneous and rectal absorption of drugs.
- Utilize different strategies to enhance percutaneous absorption.
- Design transdermal therapeutic systems.
- Formulate ointments, creams and suppositories.
- Recognize the specifications of selected cosmetic formulations

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Topical formulations

- These are preparations intended for application to the outer layer of the body such as skin and mucous membrane.
- Each preparation should have the requirements and specifications of the area of application.

Classification of topical preparations

- A- Ointments and creams
  - Skin ointments and creams.
  - Eye or ophthalmic ointments.
  - Nasal ointments and creams.
  - Rectal and vaginal ointments and creams.
  - Hair ointments and creams.

Classification of topical preparations

- B- Gels and magma
  - Skin gel Hair gel
  - Nasal and ophthalmic gel.
  - Rectal and vaginal gel
- C- Lotions
  - Skin lotions.
  - Eye and nasal lotions.
  - Vaginal douches and lotions.

Factors affecting formulation design

- 1- Nature of the site of application.
  - Anatomy, histology and physiology of the site of application.
- 2- Nature of active ingredients.
  - Physicochemical properties and stability.
  - Pharmacokinetic behaviour of the drug.
  - Inter-relation between the drug and the vehicle or base (solubility and release).
  - Interaction between the drug and vehicle or base.

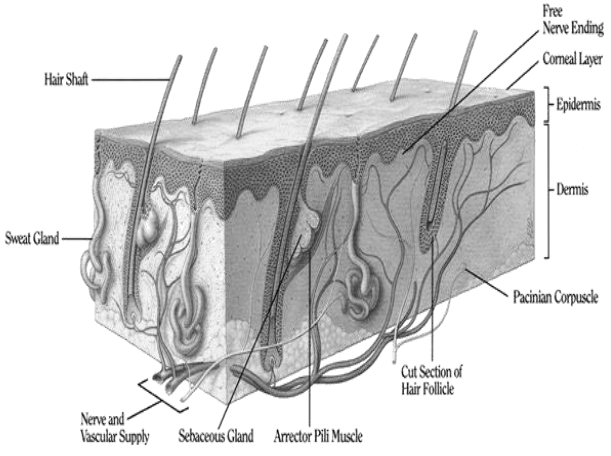
Factors affecting formulation design

- 3- Nature of the vehicle and base.
  - Type and stability of base.
  - Effect of base on the site of application.
  - Penetration capabilities of the vehicle or base.
  - Properties of additives.
  - Purpose of various additives.
  - The presence of penetration enhancer.

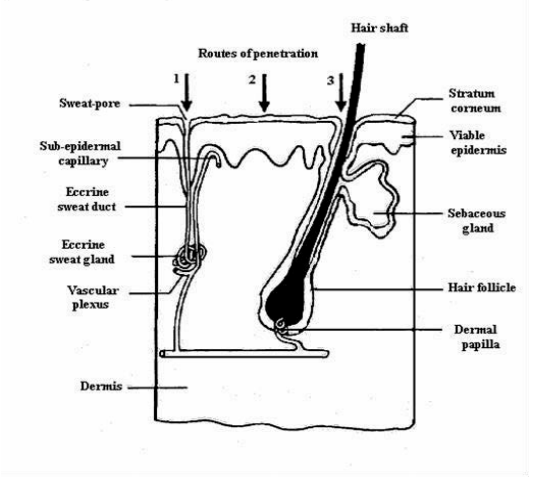
Factors affecting formulation design

- 4- Requirements and specifications of the topical formulation.
- 5- Type of disease.
  - Acute or chronic.
  - Dry or wet.
  - Superficial or deep.
- 6- Nature of the required effect.
  - Local or systemic effect.

Skin formulations:
Anatomy and physiology of the skin

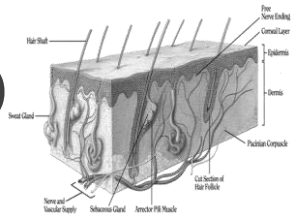


Skin structure (After Barry,1983. *Dermatological Formulations: Percutaneous Absorption,* Marcel Dekker, New York and Basel)



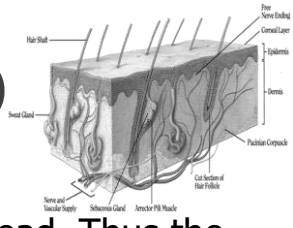
- A series of layers (epidermis, dermis and hypoderms), penetrated by hair shafts and glands.

Skin structure (cont.)
1- The epidermis



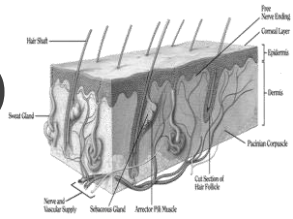
- Comprises 5 layers which from inside to outside are; stratum basal, stratum spinosum, stratum granulosum, stratum lucidium and stratum corneum (SC).
- The epidermis has no blood supply. So for any drug to reach the blood after topical application it should penetrate through the epidermis.

Skin structure (cont.)
1- The epidermis



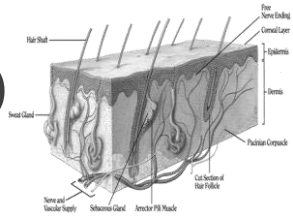
- The uppermost layer (SC) is dead. Thus the epidermis without the SC is called the viable epidermis.
- The SC is believed to be the major barrier for drug absorption (Why?).
- The basal layer differentiates and migrates upwards to form the SC.
- The basal layer contains the melanocytes.
- The water content of the skin decreases as we move from the inner layers to the surface.

Skin structure (cont.)
2- The dermis



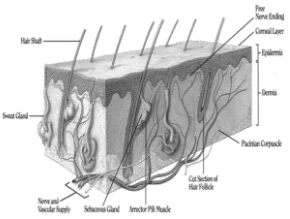
- It is a matrix of connective tissue woven from fibrous proteins (collagen, elastin and reticulin) which are embedded in amorphous mucopolysaccharides.
- Blood vessels, nerves and lymphatics traverse this matrix.
- Skin appendages are embedded into it.
- Branches from the venous plexus deliver blood to sweat glands and hair follicles.
- The blood supply to this layer acts as sink for any diffusing molecules.

Skin structure (cont.)
3- The hypodermis



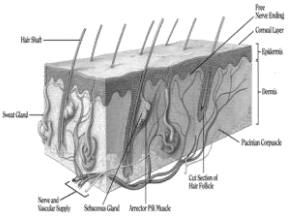
- This is subcutaneous fat which provides mechanical and thermal barrier.
- It synthesizes and stores readily available high energy chemicals.

Skin structure (cont.)
4- skin appendages



- Sweat glands: Apocrine glands
  - Mainly confined to the axillae, breast and anal-genital regions (ducts open into hair follicles).
  - Produce viscous secretion (protein, lipids and lipoprotein).
  - Secretion is good substrate for bacterial action.

Skin structure (cont.)
4- skin appendages



- Sweat glands: Apocrine glands

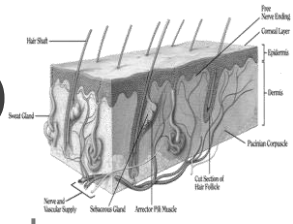
Fresh secretion (odorless)

↓ Bacterial action

Characteristic body smell.

Skin structure (cont.)

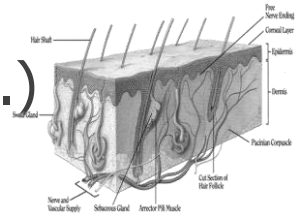
4- skin appendages



- Sweat glands: Eccrine glands
  - Numerous and distributed allover the body except lips and genital organs.
  - Their ducts open directly on the skin surface.
  - Secrete large amounts of watery secretion.
    - The secretion is not substrate for bacterial action.
    - Provides the water necessary for bacterial growth.
    - The secretion mixes with the apocrine secretion and spread the odour allover the body.

Skin structure (cont.)

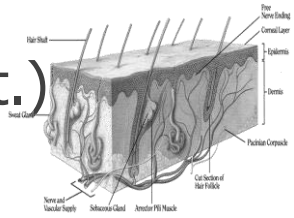
4- skin appendages



- Hair follicles
  - Develop allover the skin except the red parts of the lips, the palms and soles.
- Sebaceous glands
  - Numerous and large especially on the face forehead, ear and midline of the back ….
  - Produce sebum (glycerides, F.A, wax esters, cholesterol and its esters).
  - Abnormal activity may lead to seborrhea, gland hyperplasia and obstruction of the pilosebacous canal (acne vulgaris).

Skin structure (cont.)

4- skin appendages



- Nails
  - Like hair, the nails consist of hard keratin with high sulphur content.
  - Unlike the SC, the nails behave as hydrophilic matrix with regards to their permeability.

Target areas for dermatological formulations

- 1- Surface treatment.
  - Care for skin surface by forming protective layer, camouflage or cosmetic application.
  - E.g. protective films, sunsreens and moisturizers.
  - Can be extended to attack microorganism.
  - In case of antibiotics and deodorants, the surface organism is the target. Thus drug release is essential.

Target areas for dermatological formulations

- 2- Stratum corneum treatment
  - Mainly includes
    - Emolliency (by increasing water content).
    - Stimulating sloughing (keratolysis). e.g. with salicylic acid
  - In this type of treatment the drug must be released from the base but no penetration into the tissue is required.

Target areas for dermatological formulations

- 3- Skin appendages treatment.
  - Hyperhydrosis (excessive sweat secretion) can be treated with antiperspirant such as AL or other metal salts.
  - Acne is treated by topical exfolients {salicylic acid, tretinoin (retinoic acid) and benzoyl peroxide} and/or topical antibiotics (tetracycline, erythromycin and clindamycin).

Target areas for dermatological formulations

- 3- Skin appendages treatment.
  - Depilatories usually contains strontium or barium sulfide or thioglycolate.
  - Topical antifungal can be applied to treat fungal infection of the nails and hair.
  - In appendages treatment, targeting the drug to the skin appendages is the main problem.

Target areas for dermatological formulations

- 4- Viable epidermal and dermal treatment.
  - Many diseases can be treated provided that the preparation delivers the drug to the target area. However, many valuable drugs cannot be used topically due to poor penetration through SC.
  - So researchers started using penetration enhancers to decrease the barrier nature of SC.
  - Another approach is to use prodrug which can penetrate the SC and liberate the active part at the target site.

Target areas for dermatological formulations

- 4- Viable epidermal and dermal treatment.
  - Examples:
    - Steroidal and non-steroidal antiinflammatories.
    - Corticosteroids for treatment of psoriasis.
    - Local anesthetics decrease pain.
    - Antipruritics and antihistaminics.
    - Topical 5-fluorouracil and methotrexate can be used to eradicate premalignant and some malignant skin tumors and treat psoriasis.
- 5- Systemic treatment via percutaneous absorption (transdermal drug delivery systems, TDS)

Advantages of TDD

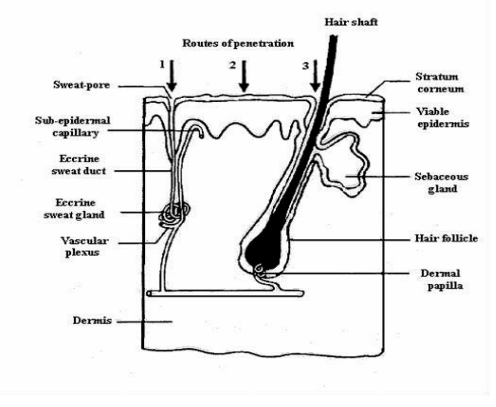
- Avoids the problems of oral route.
- Avoids the risk and inconvenience of parenterals.
- A chance for prolonged and controlled therapy after single application.
- Rapid termination of therapy is possible with easy identification of the drug in case of emergencies.

Disadvantages of TDD

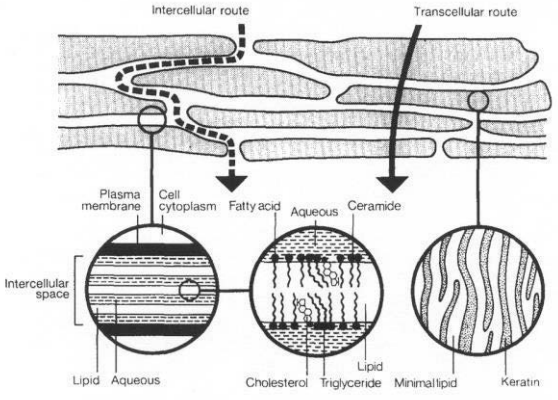
- Only suitable for potent non-irritant drugs
- Technical difficulties in adhesion to different types of skin.
- The skin is a strong barrier for drug absorption (Can we enhance TDD??)

Pathways of penetration through Skin (modified from Barry,1983. *Dermatological Formulations: Percutaneous Absorption,* Marcel Dekker, New York and Basel)

- Transepidermal pathway
  - Intercellular
  - Transcellular
- Transappendageal pathway
  - Plays minor role in transdermal drug delivery due to limited surface area.



The stratum corneum (after **Barry,** 1991, Lipid protein partitioning theory of skin penetration enhancement. *J. Control. Rel.* **15:** 237-248.)

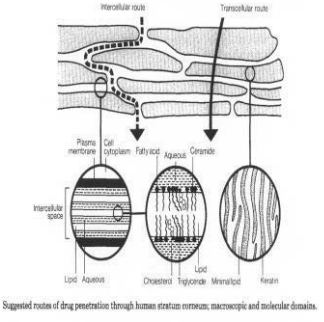


Suggested routes of drug penetration through human stratum corneum; macroscopic and molecular domains.

The stratum corneum

- The SC comprises 15-20 layers of corneocytes arranged in the so called bricks and mortar arrangement , where the keratin rich corneocytes (bricks) are embedded in the intercellular lipid-rich matrix (mortar).
- The SC contains a maximum of 20% w/w water.
- Lipids are ceramides, cholesterol, cholesterol SO4 and palmitic acid.

Model of SC lipids and cellular keratin (after **Barry,** 1991, *J. Control. Rel.* **6:** 85-97.)



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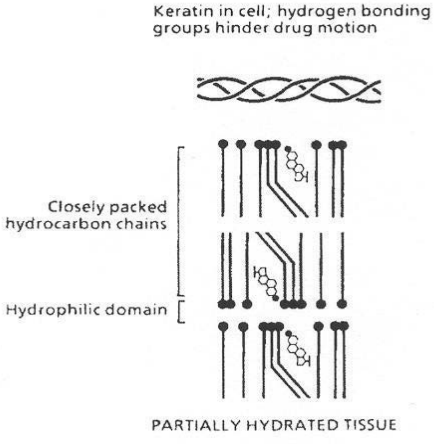


Factors affecting percutanous absorption of drugs

$$\text{Flux} = \frac{dm}{dt} = \frac{DAC}{h}$$

- dm/dt = rate of drug transport across the skin.
- D = diffusion coefficient h = thickness of skin
- A = surface area of membrane
- C = concentration in the first layer of the skin. But it is difficult to measure C. C can be approximated as:
- C = K C_o (K = partition coefficient and Co is the concentration in the donor)
- $$\text{Flux} = \frac{dm}{dt} = \frac{DKACo}{h}$$

Factors affecting percutanous absorption of drugs

$$\text{Flux} = \frac{dm}{dt} = \frac{DKACo}{h}$$

$$\frac{DK}{h} = K_p \quad \text{(Permeability coefficient)}$$

So $$\boxed{\text{Flux} = \frac{dm}{dt} = K_p A C_o}$$

Skin penetration enhancement

- Chemical methods
  - The use of chemical enhancers.
  - Optimization of thermodynamic activity and partition coefficient of drugs.
- Physical methods
  - Iontophoresis, Electroporation and Sonophoresis.
- Other methods
  - E.g. Vesicular delivery

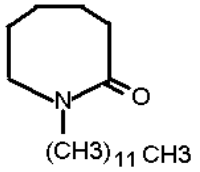
Chemical enhancers

- They can increase drug permeation by:
  - Reversible alteration of stratum corneum.
  - Increase the partition coefficient of the drug and promote its release from the vehicle.
  - Control the SC and promote drug diffusion.
  - Promote drug penetration and establish drug reservoir.
  - Increase and optimize the thermodynamic activity of the drug.

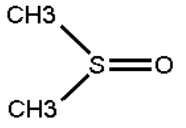
Characteristics of ideal enhancer

- Inert non-toxic, non-irritant and non-allergenic.
- It must have immediate onset of action with predictable and suitable duration.
- Once removed from the skin, the exposed tissue must recover its barrier nature.
- It should promote drug penetration and prevent loss of body content.
- It should be compatible with variety of drugs and vehicles.
- It should be good solvent for the drug.
- It should be formulated in a variety of topical formulations.
- It should be cheap, odorless and cosmetically acceptable.

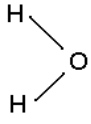
Chemical enhancers



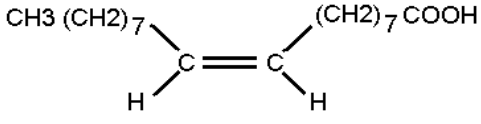
Azone



DMSO

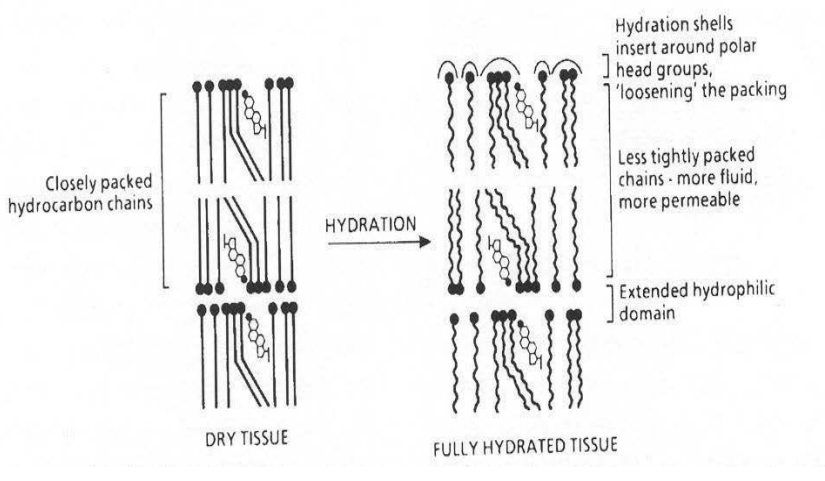


Water



Oleic acid

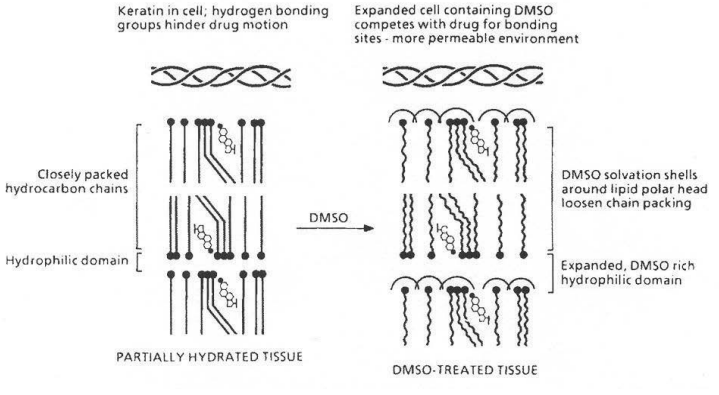
Chemical enhancers:
1- Water (after **Barry,** 1991, *J. Control. Rel.* **6:** 85-97.)



Chemical enhancers: 1- Water

- Associates via H-bonds with the polar head gps of lipids forming a shell ⟶ intermolecular forces ⟶ loose structure.
- Extends the hydrophilic domains ⟶ additional volume for drug permeation.
- Agents which promote skin hydration can be considered as enhancers (urea).

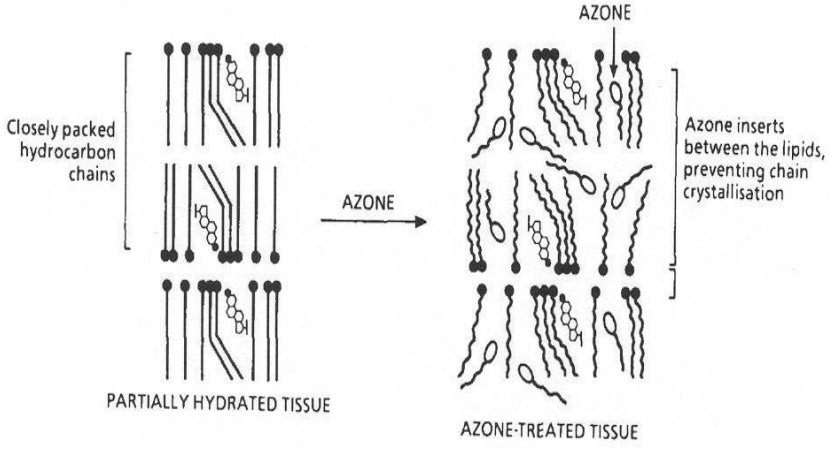
Chemical enhancers: 2- DMSO (after **Barry,** 1991, *J. Control. Rel.* **6:** 85-97.)



Chemical enhancers: 2- DMSO

- Mixes with water in all proportions.
- Can displace water which is bound to skin protein and compete with the drug for bonding sites.
- Can form solvation shells around the head gps.
- Can expand the hydrophilic regions.

Chemical enhancers: 3- Azone (after **Barry,** 1991, *J. Control. Rel.* **6:** 85-97.)



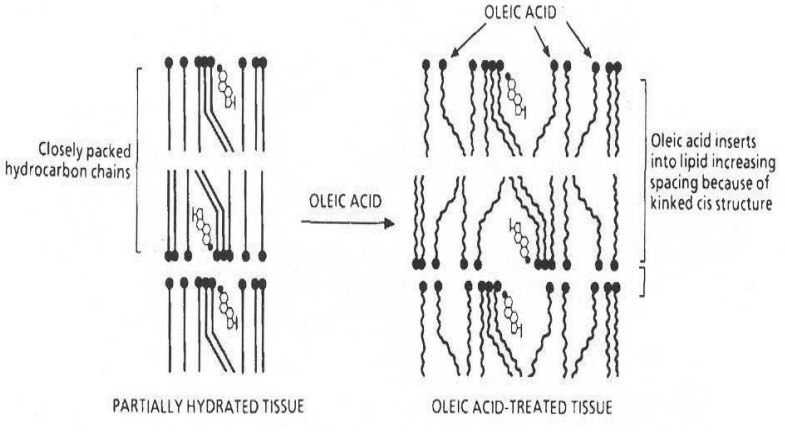
Chemical enhancers:
3- Azone

- Inserts itself between the lipid domains of the lipid bilayer of the SC

- Perturbation of the packing characteristics of skin lipid

- More loose structure.

Chemical enhancers:
4- oleic acid (after **Barry,** 1991, *J. Control. Rel.* **6:** 85-97.)



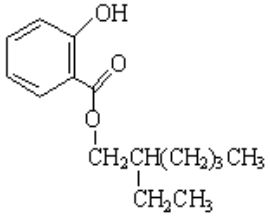
Chemical enhancers:
4- oleic acid

- Cis form is the efficient one due to its kinked structure.
- It inserts into lipids increasing the spacing due to the kinked structure resulting in more permeable arrangement.
- Oleic acid/PG combinations are more efficient (why?)

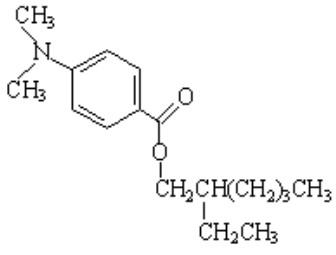
Chemical enhancers:
5- Surfactants

- Can improve absorption down the appendages by reducing the interfacial tension and emulsification of sebum.
- They can alter SC by:
  - Changing the protein helices.
  - Affecting the lipid packing.

Predict the mechanism of action of these compounds. {You can consult El Maghraby et al., International Journal of pharmaceutics, 305 (2005), 90-104}.



Octyl salicylate

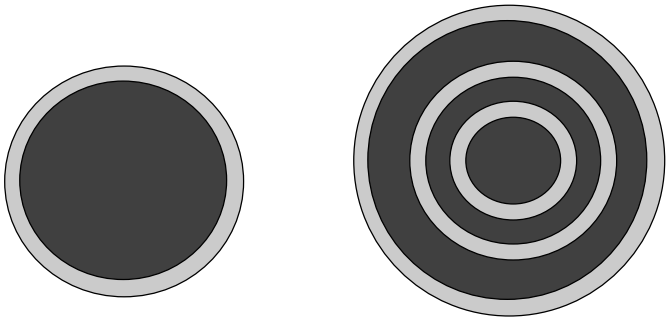


Padimate O

Liposomes

- Liposomes are simply vesicles in which an aqueous volume is entrapped in one or more lipid bilayer.
- They can carry both hydrophilic or lipophilic drugs

Liposomes types



- ULV MLV

Liposome composition

- Mainly phospholipid with or without cholesterol.
- The most commonly used phospholipid is phosphatidylcholine (PC).
- PC is an amphipathic molecule (contains both hydrophilic and hydrophobic groups) in which a glycerol bridge links a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar head group.

Schematic Representation of the basic component

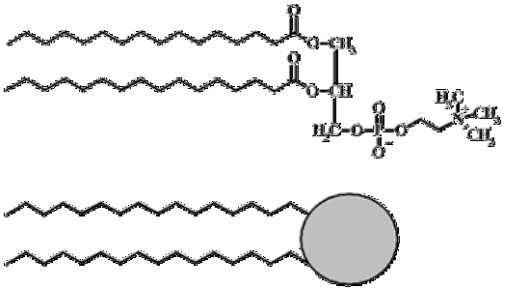
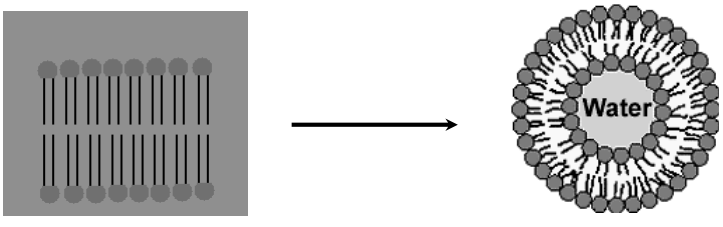


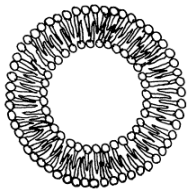
Figure 2: Chemical structure and schematic representation of a phospholipid

Liposome formation

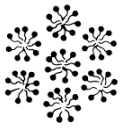


Liposomes formation

Liposome:



Typical detergent:



In the aqueous media molecules of PC align themselves in planar bilayer sheets in order to minimize the unfavorable interactions between the bulk aqueous phase and the long hydrocarbon fatty acid chains.

The double fatty acid chain is primarily responsible for bilayer formation, as compared to typical detergents with a polar head and single chain, which form micellar structure.

Liposomes: Drug Loading

- **The polar or hydrophilic drugs are entrapped in the internal aqueous compartment and the lipophilic drugs are intercalated into the liposome membrane.**

- **For lipophilic drugs the maximal incorporation or drug loading capacity depends on the concentration of lipid.**
- **For hydrophilic drug the entrapment volume is more important.**

Liposomes and skin drug delivery

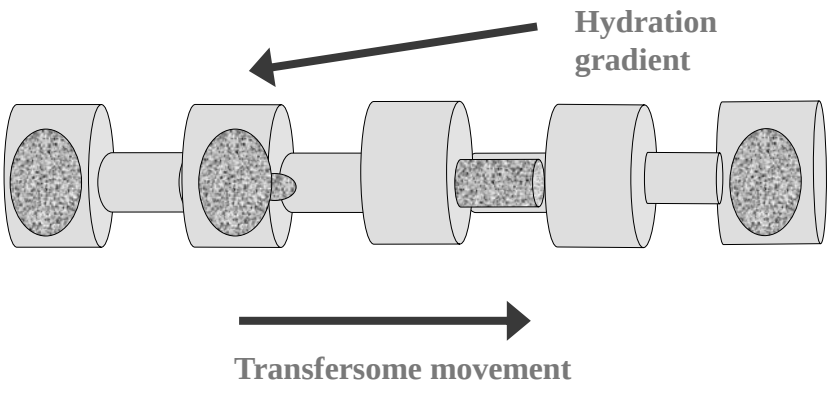
- Mezei and Gulasekharam (1980) were the first to report improved skin deposition of triamcinolone from liposomes compared to ointment.
- Cevc and Blume (1992) reported that certain type of vesicles (Transfersomes) can penetrate intact skin.

Transfersomes

- They resemble liposomes in morphology but not in function.
- They contain edge activators (e.g. surfactants).
- They are deformable.
- Xerophobia is an important characteristics.

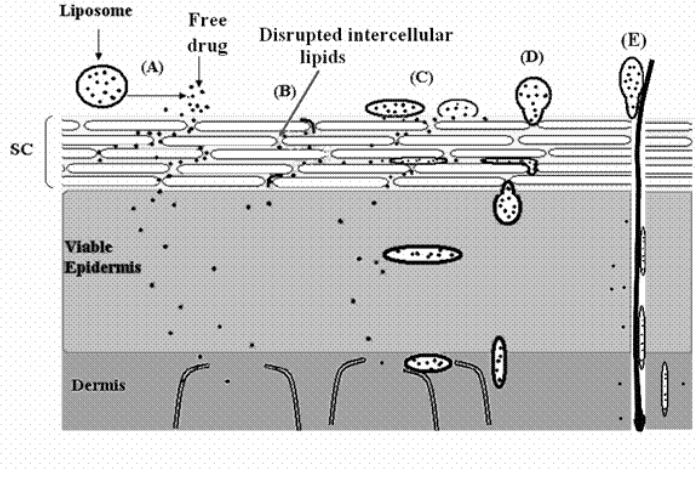
Transfersome Passing Through Pores

(after Cevc et al, Advanced Drug delivery Reviews (1996), 18, 349-378.



Mechanisms of action of liposomes as skin DDS

(Modified from: El Maghraby et al., 2008. European Journal of Pharmaceutical Sciences 34, 203–222)



Mechanisms of action of liposomes as skin DDS

(From: El Maghraby et al., 2008. European Journal of Pharmaceutical Sciences 34, 203–222)

- A- Free drug mechanism
  - In this case the drug has to be released from the vesicles before independent penetration through skin.
  - Unlikely as vesicles behave only as vehicle.
- B- Penetration enhancing effect
  - Liposome components enter the skin as monomers perturbing the packing of skin lipids.

Mechanisms of action of liposomes as skin DDS

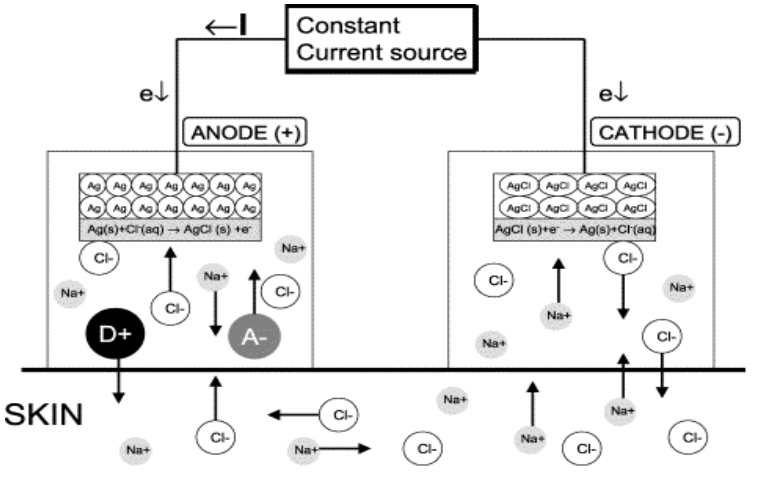
(From: El Maghraby et al., 2008. European Journal of Pharmaceutical Sciences 34, 203–222)

- C- Vesicle adsorption, adhesion and may be fusion with the skin surface
  - This at least lead to intimate contact and/or direct transfer of drug from liposomes to skin.
- D- Intact vesicles penetrate the skin
  - Xerophobia and liposome deformability provide the driving force for this mechanism.
- E- Targeted delivery to skin appendages.
  - This makes liposomes efficient in treatment of acne vulgaris

Physical enhancement: Iontophoresis

- It is the introduction of therapeutic agents into the tissue of the body by means of weak electric current (about 0.5 mA/cm^2).
- More efficient with charged (ionic) drugs.
- The dosage form of choice is hydro-gel.

Physical enhancement: Iontophoresis (from Kalia et al, 2004, *Adv. Drug Delivery Reviews*, **56:** 619-658)



Physical enhancement: Iontophoresis

- Increases the spectrum of transdermal delivery. So large molecules as peptides can be driven into the skin.
- Requires smaller application area.
- Provides higher degree of control over drug delivery rate.
- Provides a mean for non-invasive delivery.
- Less inter-patient variability.
- Control the onset of action.

Physical enhancement: Iontophoresis

- The delivery system is complicated.
- Electrochemical stability of the drug is serious problem.
- Toxicity from metal ions resulting from dissolution of electrodes is not clear.
- The delivery system is expensive.

Physical enhancement: Electroporation

- It is a transitory structural perturbation of lipid bilayers due to application of high voltage pulse.
- Electrical exposures involve electric pulses that generate trans-membrane potential of 0.5-1 volts and last for 10μs-10ms.

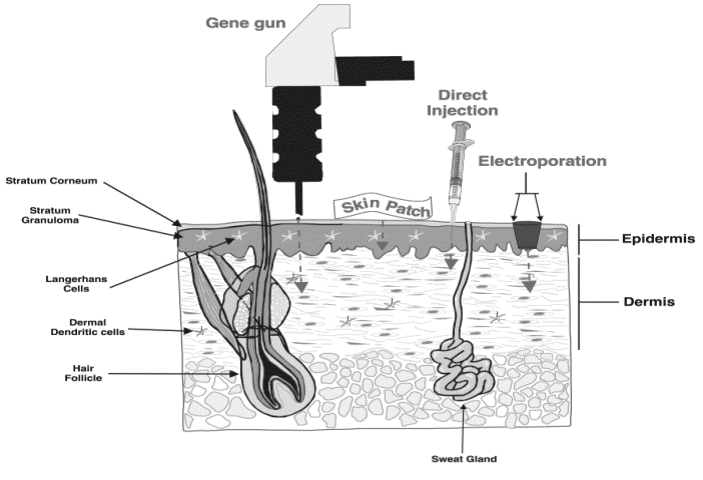
Physical enhancement: Sonophoresis

- It the movement of drug through intact skin and underlying soft tissue under the influence of ultrasound perturbation.
- Suitable for both ionic and non-ionic drugs.
- Suitable for both aqueous and oily media.

Physical enhancement: other methods

- The use of microneedles.
- The use of powder gun.

Skin-DNA immunization using different methods (From Peachman et al, 2003, *Methods*, **31**: 232-242.)



Transdermal Therapeutic Systems: Basic types

- a- Those that allow the skin to control the rate of drug absorption:
  - Release rate is higher than absorption rate.
  - Absorption is the rate limiting step.
  - Due to inter-subject variability, it is only suitable for drugs which are effective and non-toxic at a wide range of plasma concentrations.

Transdermal Therapeutic Systems: Basic types

- b- Those which control the rate of drug absorption:
  - TTS deliver drug to the skin at a rate below the rate of skin absorption, therefore penetration through the SC is not rate limiting and the device controls the rate at which the drug diffuses.
  - To be discussed in details here.

Design features and objectives of rate-controlling TTS

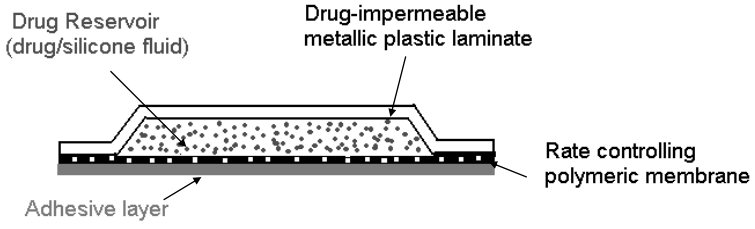
- Provide controlled rate of delivery to intact skin for absorption into the systemic circulation.
- It should have proper physicochemical properties to permit drug release and partitioning into the SC.
- It should ensure one way flux.
- It should have therapeutic advantage over other dosage forms and delivery systems.

Design features and objectives of rate-controlling TTS (cont.)

- Its adhesive, vehicle and active agent must be non-irritant and non-allergic to skin.
- The patch should adhere well to the skin and should have appropriate size and appearance.
- It should not permit proliferation of skin bacteria.

Approaches for development of rate-controlling TTS:
1- membrane moderated systems

- (After Chien, YW, Am. Heart J., 1984, **108**, 207)



Membrane moderated systems

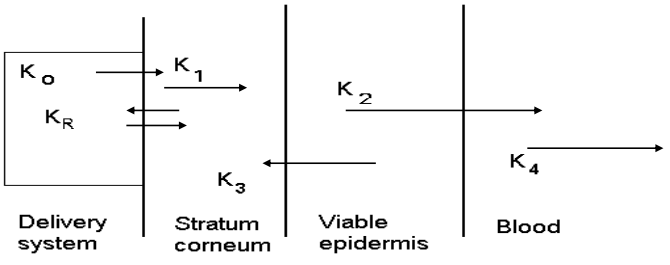
e.g Transderm Nitro (Pharma-Schwarz GmHb)

Approaches for development of rate-controlling TTS:
1- membrane moderated systems

- Drug reservoir is encapsulated in a compartment of impermeable backing and a rate controlling polymeric membrane.
- In reservoir the drug is dispersed in solid polymeric matrix or suspended in viscous liquid as silicon oil to form paste like suspension.
- The membrane is microporous (e.g. ethylene-vinyl acetate copolymer).
- On the surface of the membrane there is a layer of inert hypoallergic adhesive (e.g. silicon or polyacrylate adhesive).
- The rate of drug release can be tailored by varying the polymer composition and the thickness of the rate controlling membrane.

Approaches for development of rate-controlling TTS: 1- membrane moderated systems

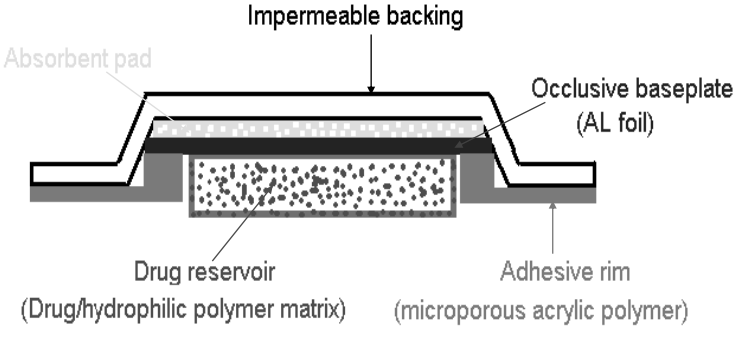
- Martin, Physical Pharmacy, p.543
- K_0 = zero order rate constant for membrane-controlled leaching of the drug
- K_R = partition between patch and the skin surface
- k_1 and k_2 = first order rate constants
- K_3= any reverse drug transport from epidermis to SC
- K_4 = first order elimination of drug from blood



Transdermal delivery of clonidine from membarne controlled patch

Approaches for development of rate-controlling TTS: 2- Matrix diffusion controlled systems

- (After Chien, Y W, Am. Heart J., 1984, **108**, 207)



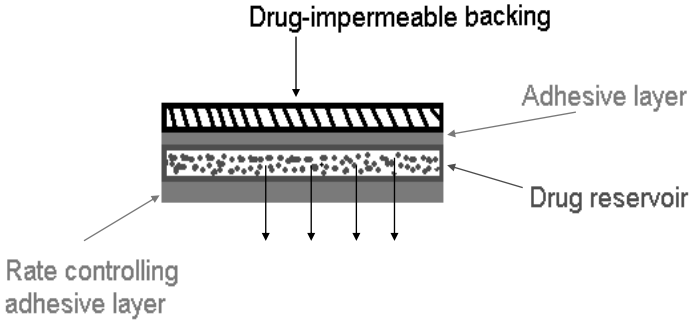
Approaches for development of rate-controlling TTS:
2- Matrix diffusion controlled systems

Consists of:

- Impermeable plastic backing
- The reservoir is formed by dispersing the solid drug in hydrophilic or hydrophobic polymer matrix. The medicated polymer is then molded into disc of defined surface area and thickness.
- Drug reservoir matrix in direct contact with skin
- The adhesive polymer is applied along the circumference to form a strip of adhesive around the medicated disc.
- Drug release is a function of the square root of time.

Approaches for development of rate-controlling TTS:
3- Adhesive diffusion controlled systems

- (modified from Martin, Physical Pharmacy, P 544)



Approaches for development of rate-controlling TTS:
3- Adhesive diffusion controlled systems

- The device consists of impermeable plastic barrier on the top, drug reservoir in the middle and several rate controlling adhesive layers next to the skin.
- The drug reservoir is formulated by dispersion of the drug in adhesive polymer then spreading the medicated polymer (by solvent casting) on metallic plastic laminate backing.
- On the top of the medicated layer, layers of non-medicated, rate controlling adhesive polymer of constant thickness are applied.
- Example: Deponit system (nitroglycerin).

Approaches for development of rate-controlling TTS:
4- Microreservoir (microsealed) systems

- In this approach, the drug reservoir is formed by suspending drug crystals in aqueous solution of hydrophilic polymer. This suspension is then dispersed in a lipophilic polymer solution by high shear mechanical force to form thousands of microspheres of drug reservoir.
- The system is rapidly stabilized by immediate crosslinking of polymer chains in situ. This produces medicated polymer discs in which the drug is sealed in microsealed system.
- The therapeutic system is produced in which the medicated disc is positioned at the centre and surrounded by an adhesive rim.

Transdermal Therapeutic Systems: Examples: Transdermal glyceryl trinitrate

Dista et al., American Pharmacy 1982 **22**, p.29

PRODUCT NAME	TYPE	SURFACE AREA (cm^2)	NTG CONTENT (mg)	NTG DELIVERED OVER 24HR
Transderm^R Nitro 5	Membrane permeation	10	25	5
Transderm^R Nitro 10		20	50	10
Nitro-Dur^R 5	Matrix Diffusion	5	26	2.5
Nitro-Dur^R 10		10	51	5.0
Nitro-Dur^R 15		15	77	7.5
Nitro-Dur^R 20		20	104	10.4
Nitro-Disc^R 16	Microsealed Polymer	8	16	11.2
Nitro-Disc^R 32		16	32	22.4

SOURCE: Dista et al., American Pharmacy 1982 22 29.

Transdermal Therapeutic Systems: Examples:

- Other clinical examples:
  - Transdermal oestradiol
    - HRT
  - Transderaml fentanyl
    - Analgesic
  - Transdermal nicotine
    - Smoking cessation
  - Transdermal testosterone
    - hypogonadism

Semisolid topical formulations
1- Skin ointment

- It is semisolid preparation intended for topical application. It contains drug in a solution or powder from.
- Ointment bases
- These can be classified chemically, physically or according to the penetration into skin.

Chemical classification:
Hydrocarbon ointment bases

- This group represents the most inert. It comprises a group of substances with a wide range of melting points. So a mixture of any desired consistency & M.P can be prepared from this group.
- They possess the least power of penetration & thus are used mainly as protective & emollient.

Chemical classification: Hydrocarbon ointment bases

- Mineral oil "paraffin oil" "Liquid paraffin"
- It is a mixture of liquid hydrocarbons obtained from petroleum.
- It is useful in levigation of insoluble powder before incorporation in oleaginous base of higher consistency.

Chemical classification: Hydrocarbon ointment bases

- **Yellow petrolatum (petrolatum jelly, yellow soft paraffin, Vaseline)**
- This is a mixture of semisolid hydrocarbon obtained from petroleum & had yellow – light amber color with meting range of (38-60ºC).
- It is frequently used as ointment base or as a constituent of emulsion base.
- It is composed of microcrystalline solid hydrocarbons. Suspended in liquid & semisolid hydrocarbon.
- It has the advantage of good consistency, stability & inertness which allow most drugs to be incorporated into it.

Chemical classification: Hydrocarbon ointment bases

- **Yellow petrolatum (petrolatum jelly, yellow soft paraffin, Vaseline)**
- It has the disadvantage of being greasy & unable to absorb or mix with water.
- (This can be solved by incorporating 15% lanolin to produce mixture which absorbs up to 50% water).
- It can be used as base for drugs particularly those which are unstable in water e.g. "penicillin, bacitracin & tetracyclines).
- It has emollient effect.

Chemical classification: Hydrocarbon ointment bases

- **White petrolatum (white soft paraffin)**
- It is petrolatum which has been bleached. It differs only from the yellow one in the colour.
- It has the same uses "but may not be suitable for eye)

Chemical classification: Hydrocarbon ointment bases

- **Parrafin wax (hard paraffin)**
- It is a purified mixture of solid hydrocarbon obtained from petroleum.
- Used to stiffen the oleaginous bases e.g. simple oint. ℞

Wool fat	50
Hard paraffin	50
Cetostearyl alc.	50
Soft paraffin	850

Chemical classification: Hydrocarbon ointment bases

- **Plastibase (Jelene)**
- It is a combination of mineral oils & heavy HCB waxes having M.W. of about 1300. The liquid part "large part" is believed to be retained in a matrix of submicroscopic interstices.
- It is a soft colorless, jellylike material which retains its consistency over a wide range of temp (-15-60^{o}C) and melts at 90-91^{o}C.
- Substances such as menthol, methyl salicylate & camphor dissolve in the plastibase. Thus ointments containing these drugs in plastibase become too soft.
- It is difficult to incorporate wax into it as it is difficult to cool the resulting mix to a smooth consistency.
- It is used as a vehicle for a dental protective paste (Orabase emollient). Orabase contains gelatin, pectin & CMC-Na in plastibase.

Chemical classification: Aliphatic alcohols

- **Monoatomic alcohols**
- This group is made up of fatty alcohols (C12-C18).
- They may be used as stiffening agents but they are mainly used for their emollient & emulsion – stabilizing properties.
- They are greaseless, forming water absorbent emulsion & render the skin smooth.
- Cetyl alcohol is the most commonly used although stearyl alc. is recommended for many bases.
- Beeler's Base & univ. of California hospital base are examples (containing aliphatic alc.).

Chemical classification: Aliphatic alcohols

- **Monoatomic alcohols**

Beeler's Base		U. C. H base	
Cetyl alc. ……..	15	Cetyl alc. ……..	6.4
White wax ……..	1	Stearyl alc. ……..	6.4
Propylene glycol …..	10	S. L. S. ……..	1.5
Sod. Lauryl SO4……	2	White petrolatum …….	14.3
Water ……..	72	Mineral oil ……..	12.4
		Water ……..	50

Chemical classification: Aliphatic alcohols

- **Polyatomic alcohols**
- These includes substances such as diethylene glycol, propylene glycol & glycerol.
- These are used with ointment containing water.
- They provide humectant action.
- Application of this group is extended after the introduction of polymers of these substance.
- Various polymers of ethylene glycol of the general formula of OHCH2 (CH**2** - O - CH**2**)n CH**2**OH are used in water removable bases.
- PEG "200-6000" are available. PEG 200-700 are liquid & any one above 700 are wax like

Chemical classification: Cyclic alcohols

- **Cholesterol and its alcohols and esters**
- applied as bases for their emollient properties.
- **Anhydrous wool fat**
- It is the purified anhydrous fat like substance derived from the wool of the sheep.
- It consists mainly of fatty acid esters of cholesterol, lanosterol & fatty alcohol.
- They have good ability to absorb twice its weight of water forming w/o emulsion.
- Various modifications of wool frat can add some advantage to it e.g. liquid lanolin (a mix of liquid esters derived from the fractionation of wool fat) is less sticky.
- Also polyoxyethylene derivative of wool fat is water soluble.
- Hydrogenated wool fat is not sticky.

Chemical classification: Cyclic alcohols

- **Hydrous wool fat**
- Semisolid fat like substance.
- It is w/o emulsion that contains 25-30% water.
- Additional water may be incorporated by mixing.
- Generally hydrous & anhydrous lanolin are mixed with petrolatum to form hydrophilic petrolatum.
- In some cases cholesterol replaced lanolin to avoid the potential sensitizing effect of lanolin on skin.
- Formulations with high conc. of cholesterol allow incorporation of water.

Chemical classification: Cyclic alcohols

- **Wool alcohol**
- Is crude mix sterols & triterpene alcohols prepared by treating wool fat with alkali & separating the fraction containing cholesterol & other alcohol.
- It may replace lanolin in base (wool alcohol oint)

Wool alc. oint

℞

Wool alc. 60
hard paraffin 240
soft paraffin 100
liquid paraffin 600

Oily cream

℞

Wool alc oint 50
Water 50

Chemical classification: Acids

- Acids having 12-18 carbon atoms can be used.
- They are used as a source of free acids to react with alkali to form a soup (vanishing cream).
- In a few cases stearic acid is used as stiffening agents.

Chemical classification:

Esters of monatomic alcohol "monohydric"

- **Aliphatic**
- This group includes yellow & white beeswax, carnauba wax and spermaceti.
- They are used generally to increase consistency of ointment (5%).
- They contain mainly esters of fatty acids & fatty alcohol.
- For beeswax & carnauba wax there are some free fatty acids as well which is desirable for cold cream.

Chemical classification:
Esters of monatomic alcohol "monohydric"

- **Cyclic**
- This mainly contains fatty acid esters of cholesterol & oxycholesterol.
- They are used with fatty alcohol to provide the hydrophilic properties of petrolatum.

Chemical classification:
Esters of polyhydric alcohols

- Triglyceride esters are the only naturally occurring.
- Other members of this group are synthetic.
- Synthetic esters are usually mixtures of mono, di & sometimes tri esters.
- They have weak emulsifying properties & thus they have to be mixed with soap to increase the emulsifying power.
- Thus glyceryl monostearate (G.M.S) is available as non-emulsifying base & as self emulsifier (mixed with soap e.g. sod. Stearate)

Chemical classification: Vegetable oils

- Olive oil, almond oil, sesame oil, corn oil are used in ointment to decrease the M. P. and to increase the emolliency.
- Oils can be also used in preparations containing high percentage of powder. Thus zinc oxide is prescribed with olive oil or caster oil.
- They are used extensively in cosmetics.
- Castor oil differs from others in that it contains hydroxyl fatty acids. It is the only veg. oil that dissolves in ethanol.
- They can be hydrogenated to decrease the incidence of rancidity.

Chemical classification:

- Polyoxyethylene sorbitan esters (Tweens)
- e.g polysorbate 80 "polyoxyethylene sorbitan monooleate" (Tween 80).
- These are miscible with water & can form o/w emulsion.
- Sorbitan esters (Span)
- These are partial F. A. esters of sorbitan.
- They are less miscible with water thus form w/o emulsion.

Chemical classification:

- Examples containing Tween or Span
- w/o base.
- R/ Petrolatum 90
- Arlacel 83 (sorbitan sesquioleate) 10
- Arlacels are the same as spans but are processed to provide light colour.
- This formula can be used as ointment base or water can be added to it to provide w/o emulsion.

Chemical classification:

- Examples containing Tween or Span
- O/w ointment base
- R/ Cetyl alcohol 20
- Mineral oil 20
- Tween 80 ..... 4.5
- Arlacel 80 ..... 0.5
- Water 55

Chemical classification:

- Polyoxyethylene Fatty acid Esters (Myrjs)
- e.g. Polyoxyl40 stearate.
- They are dispersible in water. They can form o/w emulsion.
- Polyoxyethylene fatty alcohol ethers (Brij)
- Due to absence of ester bond, this group can work in both acidic & alkaline pH.

Chemical classification: Soaps

- Sodium, Ammonium & potassium oleate or stearate are the most commonly used soaps.
- Calcium & magnesium salts are sometimes used.
- Soaps may be used as such (preformed) or it may be produced in situ after chemical reaction.
- Sod. or pot. stearates when formed by the reaction of stearic acid with sod. or pot. bases in presence of oils, water & waxes will yields vanishing cream bases.
- Calcium oleate when formed by mixing olive oil & lime water and adding calamine & zinc oxide, will produce calamine cream.

Chemical classification: Soaps

- Soaps formed by the reaction of fatty acids (e.g. stearic) & triethanolamine are widely used in modern dermatological formulators.
- They are less irritant to skin compared with metallic soaps.

- Example for vanishing cream base.
- **R/** Stearic acid 15
- White wax 2
- White petrolatum..... 8
- Triethanolamine 1.5
- Propylene glycol 8
- Water 65.5

Chemical classification: Silicones

- These are a series of synthetic polymers in which the basic structure is not carbon but a chain of alternating silicon & oxygen atoms (e.g. -O-Si-O-Si). Each Si atom is attached to one or more organic groups, such as methyl or methyl phenyl group.
- Examples:
  - Dimethylpoysiloxanes (DC 200) (Dimethicone)
  - Methyl phenyl polysiloxane (DC 556)

Chemical classification: Silicones

- **Dimethylpoysiloxanes (DC 200) (Dimethicone)**
- These are the most commonly known silicones.
- They are clear fluids & are available in a wide range of viscosities.
- They are water repellent & can resist changes in heat & oxidation.
- These properties make them very useful in preparations for the management of dermatologic disorders in which protection from moisture is indicated.
- Silicone ointment containing 30% DC200 in petrolatum was found effective in treatment of skin irritation & diaper rash.

Chemical classification: Silicones

- **Methyl phenyl polysiloxane (DC 556)**
- It is a fluid having the same characteristics of silicone fluids. In addition to this, it is soluble in 95% ethanol & has greater compatibility with organic substances.
- It is used in protective creams & lotions, aerosol hair sprays & shaving lotion.
- Silicones are non-toxic, non-irritating & non-sensitizing.
- They can be mixed with other substances to form silicon-based absorption or emulsion bases.

Physical classification

- **1- Oleaginous bases**
- These include hydrocarbon bases, natural triglycerides and vegetable oils.
- **2- Absorption bases.**
- These are usually anhydrous bases w' have the property of absorbing several times their weight of water forming emulsions.
- Hydrophilic petrolatum U.S.P & anhydrous lanolin U.S.P are abs. bases as additional water can be included.
- Lanolin & cold cream are examples of this type.
- Absorption bases vary in their composition, but they are mainly mixtures of cyclic alcohols with petrolatum.
- Examples: Aquabase
- R/ Cholesterol 30
- Cottonseed oil 30
- White petrolatum 940

Physical classification: 3- Emulsion bases

- **W/O emulsion base (Cold cream base)**
- They are used as emollients where the aqueous phase hydrates the skin & the oily phase forms an occlusive covering which prevents water loss due to evaporation.
- Not water removable.
- These bases are also used as vehicles for medicinal agents such as sulfur, ammoniated mercury, balsam Peru, zinc oxide .....
- Cold creams are defined as emulsions made up of oil (40-70%), wax or spermaceti (5- 15%) & water (20-35%). The name cold cream referred to the cooling effect produced by the slow evaporation of water after application to skin
- R/ Mineral oil 50
- Beeswax 14
- Borax 0.7
- Purified water 35.3

Physical classification: 3- Emulsion bases

- **O/W emulsion bases (vanishing cream bases)**
- Used as base for medicaments.
- They are water removable. This is excellent advantage for this type of bases especially if it is going to be applied to hairy skin, such as scalp.
- Vanishing creams are also used in cosmetics.
- Although they contain significant amount of oil phase, the residue left after evaporation of water is soft in appearance & does not feel greasy.
- Vanishing creams can be used as hand creams, & as foundations to provide a suitable substrate for powders & other makeup.
- Example R/
- Stearic acid 15
- Petrolatum 13
- KoH 0.5
- Water 100

Physical classification: 3- Emulsion bases

- **O/W emulsion bases (vanishing cream bases)**
- Due to high water content of vanishing cream bases, they are dispensed in tubes or tightly closed jars.
- In addition, humectants like glycerol or propylene glycol may be added to prevent evaporation of water.
- Many emulsion bases contain fatty alcohols (cetyl &/or stearyl alcohol) which add stability to the emulsion & potentiate the water number.
- e.g.
- R/ Cetyl alcohol 5
- Stearyl alcohol 5
- White petrolatum 20
- Sod. lauryl sulphate 1
- Propylene glycol 8
- Purified water 61

Physical classification:
3- Emulsion bases

- **O/W emulsion base (vanishing cream base)**
- **The B. P & B. P. C contain formulae for emulsifying bases that produce o/w emulsions on addition of water.**
- **examples include cetomacrogol (PEG 1000 monocetyl ether) emulsifying wax (BPC) & cetomacrogol emulsifying oint. (BPC).**
- **Also Emulsifying wax & ointment (BP) is used to prepare aqueous cream.**
- **Emulsifying Wax (BP)**
- **R/ Cetostearyl alc 90**
- **S. L. S 10**
- **Water 4**
- **Emulsifying oint (BP)**
- **R/ Emulsifying wax 300**
- **White soft paraffin..... 500**
- **Liquid paraffin 200**
- **Aqueous cream**
- **R/ Emulsifying oint 300**
- **Chlorocresol 1**
- **Water 690**

Physical classification:
4- Water soluble bases

- Water - soluble ointment bases include those bases prepared from carbo waxes (polyethylene glycols, PEGs).
- Carbo wax 200 - 600 clear liquid.
- Carbo wax 1000 - 6000 white waxy solids.
- They are nonionics & water soluble.
- Carbo wax (PEGs) can be blended with a variety of water removable bases with consistency varying from soft to Hard.

Physical classification:
4- Water soluble bases

- **Polyethylene glycol ointment (U. S. P).**
- This is a blend of carbo waxes 4000 & 400. Due to high degree of water solubility, the maximum amount of water to be incorporated in this formulation is 5%.
- If higher proportion of water is to be incorporate the following formula will be helpful
- R/ Carbowax 4000 …….. 47.5
- Carboax 400 …….. 47.5
- Cetyl alcohol …….. 5

Classification according to the degree of penetration into skin

- **1- Epidermic ointment bases.**
- These demonstrate no or very slight power of penetration into skin.
- These are indicated especially if the therapeutic effect is to be exerted on the diseased epithelium.
- This group includes bases which contain petrolatum, waxes & their combinations

Classification according to the degree of penetration into skin

- **2- Endodermic ointments bases**
- These bases have some power of penetration into the deeper layer of the skin.
- These include softer bases which liquefy at the body temp such as vegetable oils, lanolin, anhydrous lanolin or combinations.
- **3- Diadermic ointment bases**
- These are bases which penetrate the skin, thus offering better opportunity for absorption of drug.
- This group includes ointments of emulsion type or water-soluble bases.

Selection of appropriate ointment base

- The selection of base for formulating ointment depends on careful assessment of the following factors:
- 1- The desired rate of release of drug from the ointment.
- 2- The desirability for enhancement of percutaneous absorption.
- 3- The requirement of occlusion of skin & protection from moisture.
- 4- The short & long term stability of drug in the base.
- 5- The influence of the drug on the physical properties of base "e.g. consistency".

Selection of appropriate ointment base (Continue)

- 6- The nature of the required effect.
- 7- Patient factor "skin condition" e.g. oozing or dry, may affect the selection of the base.
  - As a general rule, if the patient skin is wet, we must dry it & if it is dry we shall wet it.
  - So if the patient skin is dry, an occlusive ointment base which will retain moisture will be preferable, & vise - verse.
  - Accordingly, it should be clear that ointment & cream bases are not interchangeable & the dermatologist must consider & utilize the effect of the base as much as the affect of the active ingredient

Preparation of ointment

- A) Cold method "incorporation"
- B) Fusion method
- These methods utilize:
- - Slab & spatula [stainless steel spatulas may be used except for some drugs which will interact with the metal (e.g. iodine & mercury salts)]. For these special drugs, hard rubber spatula may be used.
- - Mortar & pestle (used when large quantities of liquids are to be incorporated in the ointment or if large quantity of ointment is required.
- - For large scale production ointment mill or any other suitable mixer can be used (to be studied in the industrial pharmacy courses).

Preparation of ointment: General notes

- 1- Insoluble substances must be in a very fine form. They are best incorporated when levigated with small portion of the base "liquid or melted base".
- 2- Water soluble salts can be incorporated by dissolving them in a small amount of water & incorporating in the base using anhydrous lanolin.
- 3- Fusion is necessary when waxes or wax like materials are present in the formulation.
- 4- Fusion is used also when the drug is soluble in the melted base.
- 5- Fusion must be performed according to descending order of melting points.

Ingredients requiring special consideration

- **Alcoholic solution**
  - Small quantities of highly alcoholic solution "e.g. cool tar" can be incorporated directly in many water-containing emulsion bases. However, it is advisable to evaporate the alcohol before incorporation in oleaginous.
- **Aqueous solutions**
  - These can be incorporated readily in absorption base
  - e.g. prepare the following ointment
  - R/ Iodine ……..... 1
  - Petrolatum to ……. 50
  - N.B. I_2 + KI = KI_3 (soluble complex)

Ingredients requiring special consideration

- **Alkaloids**
  - Salts can be dissolved in the least amount of water & incorporated in absorption base.
  - Alkaloidal base can be powdered & levigated with suitable levigating agent before incorporation into the base.
- **Cool Tar**
  - It is viscous liquid obtained as a by - product during destructive distillation of cool.
  - It is incorporated in a base containing tween 80. Tween serves dual function → improves dispensability of tar in the ointment & aids in the removal of ointment from the skin. Cool tar can be easily incorporated in emulsion bases.

Ingredients requiring special consideration

- **Antibiotics**
- Anhydrous bases such as petrolatum & white ointment are employed as vehicles for antibiotics such as penicillin's, bacitracin, chloramphenicol & tetracycline. These antibiotics are rapidly inactivated in water - containing bases.
- - Surfactants can inactivate bacitracin slowly - but water or water - containing base, propylene glycol and PEG 400 lead to rapid inactivation of bacitracin.
- - Neomycin S04 is stable in aqueous solution & water containing bases.
- - Polymyxin B sulfate is stable in aqueous solution & in petrolatum or PEG bases.
- **Resinous substances**
- Can be levigated with castor oil, before incorporation in oleaginous base.

Containers

- The two commonly used containers are the ointment Jar & collapsible tubes.
- The Jars are available in glass or plastic. The glass is either transparent, green, amber or opaque white.
- Collapsible tubes made of tin reduce the oxidation to minimum as only small surface area is exposed.
- The tubes are available with special tips e.g. eye tips, nasal tips, vaginal & rectal tips.
- Recently for tooth gels, high viscosity pumps with dispensing closures are available.

Ophthalmic preparations: Ocular drug delivery

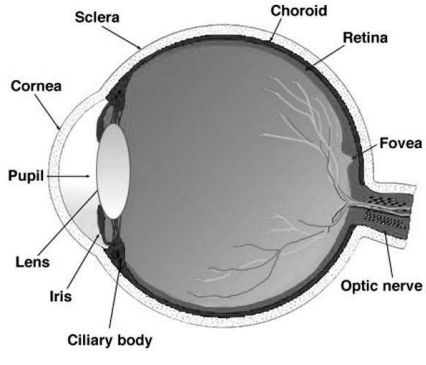
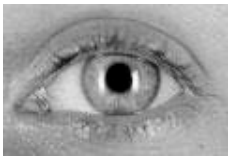
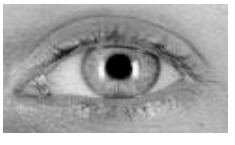


Fig. 6. Vertical sagittal section of the adult human eye.

Ocular drug delivery



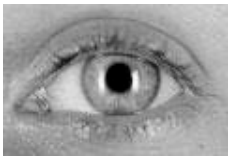
- Blinking
- High tear turnover ⟹ Rapid pre-corneal loss.
- Transconjunctival absorption.
- Drainage via the nasolacrimal duct before transnasal absorption.
- Precorneal tear film.
- Poor corneal permeability.
- Only 5% of the applied eye drops penetrates the cornea.
- Multiple applications ⟹ Side effects



Strategies to enhance ocular delivery

- Application of simple ointment.
- Collagen shields
- Medicated contact lenses
- Gels and
- In situ gelling systems:
  - Thermosensitive.
  - pH dependent.
  - Ion activated.
- Fluid colloidal systems

Ocular drug delivery



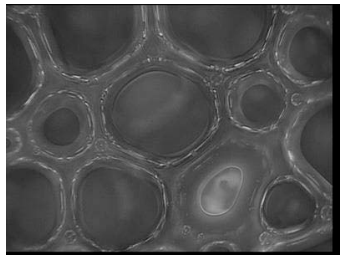
- Accordingly, the challenging objective is to develop topical ocular delivery systems with improved ocular retention, increased corneal drug absorption and reduced systemic side effects, whilst maintaining the simplicity and convenience of the dosage form as eye drops.

Ophthalmic ointments

- These are ointments intended for application to the eye.
- The vehicle for these ointments must be nonirritating & sterile.
- Emulsion bases may be irritating due to the presence of surfactant or other emulsifier in the base.
- Petrolatum / mineral oil or petrolatum / lanolin are often used due to their low irritating potential.

Gels

- Two-component semisolid systems rich in liquid.
- The characteristic feature of gels is the presence of a continuous structure providing solid like properties.
- In a polar (hydrophilic) gel, polymer molecules aggregate forming a three-dimensional net work in which the hydrophilic phase (water) is entrapped.
- In an oleo-gel the entrapped liquid within the network is oily.



Gel

- They are concentrated polymers solutions that exhibit high viscosity due to interaction of polymer chains in a three dimensional fashion in the bulk of solvent.
- Polymer-solvent system containing 3D network of stable bonds. The network could be formed due to chemical or physical bonds.

Gels

- Interaction between polymer molecules forming the gel net work could be due to physical (hydrogen bonding or Van der Waal) or chemical (covalent bonds).
- When a gel is formed the system is characterized by a critical gellation concentration (of the polymer) below which a gel is not formed. This concentration varies depending on the nature of the solvent and solvent polymer interaction.

Gels

- According to the BP, gels could be classified into 2 categories:
  - Hydrophobic gels (oleogels): Where liquid paraffin or other fatty oils are gelled with colloidal silica (polymer) or aluminum or zinc soaps (surfactants).
  - Hydrophilic gels (hydrogels): In which water, glycerol or propylene glycol are gelled with a suitable gelling agent (poly vinyl alcohol, cellulose derivative, starch, tragacanth etc).

Gel – summary

- Gel = solvent + gelling agent (polymer or surfactant).
- Gelling occurs when molecules of the polymer or surfactant are in sufficient concentration to associate forming a 3D net work in which the solvent is entrapped. The association could be physical or chemical.
- The process where by gels may contract on standing and some of the solvent is squeezed out is called synerisis (bleeding) and is a problem with long term stability of gels.

Preparation of gel

- Dispersion followed by gel formation upon standing
  - Cellulose derivatives (methyl cellulose, CMC and HPMC) can form lumps in cold water so they can be dispersed boiling water (2/3 of the solvent) and adding the rest as cold water.
  - Carbopol undergoes pH dependent gel formation.
  - Alginates undergoes ion triggered gel formation.

Pasts

- Semisolid dosage forms containing as much as 50% powder dispersed in a base.
- They are less greasy than an ointment due to reduced amount of base used. However they are stiffer and more difficult to apply and spread.
- The high solid content in pastes is advantageous as it renders them of particular use in absorbing noxious secretions (nappy rash in babies) or to provide the required cleansing action as in toothpastes.

Pasts

- Extemporaneous preparation:
- Similar to an ointment (slab and spatula) however the levigating liquids are avoided as it may compromise the final consistency of the paste.

suppositories and pessaries

Objectives

At the end we will be able to:

1. ***Define suppositories and pessaries.***
2. ***Classify suppositories***
3. ***Differentiate between suppositories and pessaries.***
4. ***Advantages & disadvantages of suppositories.***
5. ***Discuss different suppository bases used.***
6. ***Discuss the different methods of preparation***

Introduction

- ***Some medicines are formulated to be used in the body cavities: the suppository (for the rectum), the pessary (for the vagina) and the bougie (for the urethra or nose).***
- ***The basic method of manufacture was the same for each preparation, but the shape differed.***
- ***Suppositories were "bullet" or "torpedo" shaped, pessaries "bullet" shaped but larger and bougies long and thin, tapering slightly***

Dosage form characteristics

a. Rectal suppositories

- ***For adults weigh 2 gm and are torpedo shape.***
- ***Children's suppositories weigh about 1 gm.***

b. Vaginal suppositories or Pessaries

- ***Weigh about 3-5gm and are molded in globular or oviform shape or compressed on a tablet press into conical shapes.***

c. Urethral suppositories

- ***Called bougies are pencil shape.***
- ***Those intended for males weigh 4 gm each and are 100-150 mm long.***
- ***Those for females are 2 gm each and 60-75 mm in length.***

Dosage form characteristics

d. Nasal suppositories:

- ***Called nasal bougies or buginaria meant for introduction into nasal cavity.***
- ***They are prepared with glycerogelatin base.***
- ***They weigh about 1 gm and length 9-10 cm.***

e. Ear cones:

- ***Aurinaria and meant for introduction into ear.***
- ***Rarely used***
- ***Theobroma oil is used as base.***
- ***Prepared in urethral bougies mold and cut according to size.***

Rectal route for drug administration

- ***The patient is unable to use the oral route (infection of GIT, nausea, unconsciousness, post-operation and young, old and mentally disturbed patients).***
- ***The drug is less suited for oral route (causes GI side effects, insufficiently stable at pH of GIT, susceptible to enzymatic degradation, has first-pass effect, with unacceptable taste)***

Drawbacks of rectal route

- ***Slow and incomplete absorption.***
- ***Inter and intra-subject variation.***
- ***Development of proctitis.***
- ***Problems with large scale production of suppositories and of achievement of a suitable shelf life***
- ***Demanding stringent storage conditions.***

Therapy with the rectal route

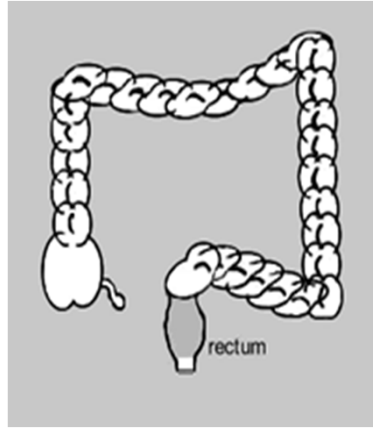
- ***Local effect:***

1. ***In case of pain, itching and haemorroids***
2. ***locally active drugs include astringents, antiseptics, local anaesthetics, vasoconstrictors, anti-inflammatory compounds, soothing and protective agents and some laxatives.***

- ***Systemic effect:***

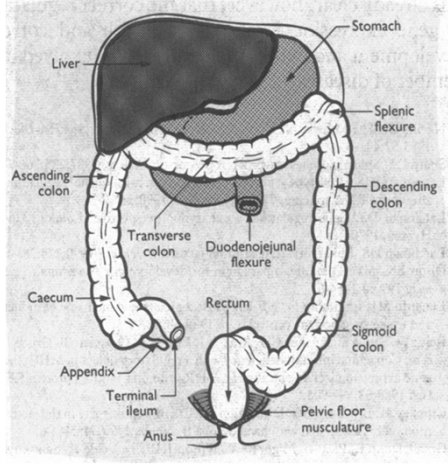
Anti-asthmatics, anti-rheumatics and analgesics.

Anatomy and Physiology of Rectum



- ***The rectum is about <u>15 to 20 cm</u> long.***
- ***It hooks up with the sigmoid colon to the north and with the anal canal to the south.***
- ***It is a hollow organ with a relatively <u>flat wall surface</u>, <u>without villi</u> and with only three major folds, the rectal valves***

Anatomy and Physiology of Rectum (cont.)

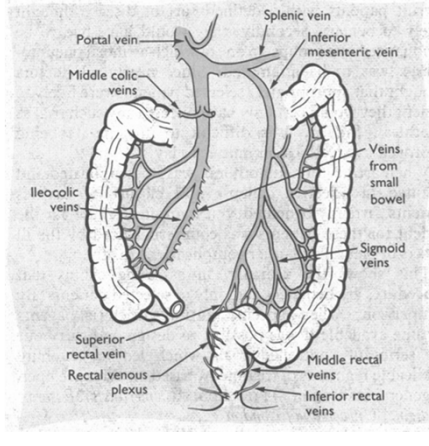


- ***The terminal 2 to 3 cm of the rectum is called the anal canal.***
- ***The opening of the anal canal to the exterior is called the anus.***
- ***The anus is controlled by an <u>internal sphincter of smooth muscle and an external sphincter of skeletal muscle.</u>***

Anatomy and Physiology of Rectum (cont.)

- ***Under normal conditions, the rectum is empty and filling provokes a defecation reflex which under voluntary control.***
- ***The transverse folds in rectum keep stool in place until the person is ready to go to the bathroom. Then, stool enters the lower rectum, moves into the anal canal, and then passes through the anus on its way out.***
- ***Rectum contains about 2 to 3 ml of mucous, which <u>has a pH of 7.4 and little buffering capacity.</u>***

Anatomy and Physiology of Rectum (cont.)



- ***The rectal tissues are drained by <u>the inferior, middle and superior haemorrhoidal veins</u>,***
- ***Only the <u>superior vein connects with the hepatic-portal system.</u>***

Anatomy and Physiology of Rectum (cont.)

- ***Therefore, due to the inability of the fluids within the rectum to alter the degree of ionisation, the salt form of the drug is an important determinant of the resulting local efficacy and/or systemic absorption.***
- ***The presence of faecal matter will markedly affect both the dissolution and absorption of the drug***
- ***Following absorption from the rectum, the therapeutic agent enters the haemorrhoidal veins.***
- ***Blood from the upper haemorrhoidal vein enters the portal vein, which flows into the liver, where drug metabolism occurs. Conversely, blood in the middle and lower haemorrhoidal veins enters the general circulation***

Absorption of drugs from the rectum

- ***Medicaments absorbed in the lower part of the rectum are delivered directly into the systemic circulation, thus avoiding any first-pass metabolism.***
- ***However, it has been found that suppositories can settle high enough in the rectum to allow at least some drug absorption into the superior vein.***
- ***Thus keeping the drug in the lower part of the rectum would be advisable***
- ***Insertion of a suppository into the rectum results in a chain of effects leading to the bioavailability of the drug.***

Absorption of drugs from the rectum

- ***Depending on the character of the base, a suppository will either dissolve in the rectal fluid or melt on the mucous layer.***
- ***Since the volume of rectal fluid is so small, complete dissolution of the base require extra water.***
- ***Due to osmotic effects of the dissolved base, water is attracted with a painful sensation for the patient.***
- ***Independent on the base type, dissolved drugs in the suppository will diffuse out towards the rectal membrane.***
- ***The process of absorption will be passive diffusion.***

Absorption of drugs from the rectum

- ***Examples of the classes of drugs that are administered by the rectal route for systemic absorption include:***

– antiemetics (e.g. prochlorperazine)

– analgesics (e.g. oxymorphone hydrochloride)

– anti-inflammatory agents (e.g. indomethacin)

– ergot alkaloids.

- ***There are no esterases or peptidases in the rectal fluid.***
- ***Local muscle activity within the rectal wall may influence the rate of dissolution of solid dosage forms within the rectum, i.e. suppositories***

Physiological factors in rectal absorption

1- Quantity of fluids available

- ***Very small volume under normal conditions (3ml spread in a layer of approximately 100 µm thick over the organ).***
- ***Under non-physiological conditions (osmotic attraction of water by water soluble base or diarrhea), the volume is enlarged.***
- ***Thus, absorption of slightly soluble drugs (i.e. phenytoin) will be dissolution rate limited.***

2- Properties of rectal fluids

- ***Composition, viscosity, pH and surface tension of rectal fluids have great effects on drug bioavailability.***

Physiological factors in rectal absorption

3- Contents of the rectum

- ***Faecal content***

4- Motility of the rectum

The rectal wall may exert a pressure on a suppository present in the lumen by two distinct mechanisms.

- ***First, the abdominal organs may simply press on to the rectum when the body in upright position. This may stimulate spreading and promote absorption.***
- ***Second, the motility of the rectal muscle associated with the presence of food in the colon (waves of contractions running over the wall of the colon)***

Physiological factors in rectal absorption

5. Site of absorption within the rectum

The site of absorption will affect the fate of the therapeutic agent within the blood stream (first-pass metabolism will occur following rectal administration but with lower extent when compared to drug absorption following oral administration)

6. The partition coefficient and degree of ionisation of the therapeutic agent

Some rectal products are lipophilic and if the therapeutic agent is also lipophilic, the release of the drug will be slow and the solubility of the drug in the rectal fluids will be low

Conversely, the use of (dispersed) hydrophilic drugs in lipophilic bases is preferred because of greater thermodynamic tendency to dissolve in the rectal fluid.

Physiological factors in rectal absorption

7. The particle size of the dispersed active agent

If the formulation is composed of an active agent that has been dispersed in the appropriate formulation base/vehicle, e.g. a hydrophilic drug dispersed in a lipophilic base or vice versa, the rate of dissolution of the drug is inversely proportional to the particle size of the dispersed active agent.

A reduction in particle size of the dispersed therapeutic agent will also affect the physical stability of the formulation

Definition

- ***suppositories are solid dosage form meant to be inserted into body cavity like rectum, urethra, vagina where they melt or soften to release the drugs & exert local or systemic effect."***
- ***The medicament is incorporated into a base such as cocoa butter which melts at body temperature, or into one such as glycerinated gelatin or PEG which slowly dissolves in the mucous secretions.***
- ***Suppositories are suited particularly for producing local action, but may also be used to produce a systemic effect or to exert a mechanical effect to facilitate emptying the lower bowel***
- ***Shapes available : cone, bullet, torpedo***

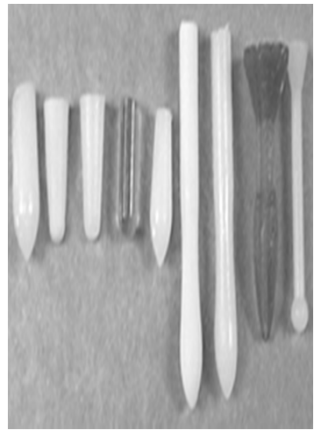
Advantages

1. ***Alternate dosage form for the drugs with less bioavailability when taken orally.***
2. ***Drugs having bad odor & taste.***
3. ***For treating unconscious & vomiting patients***
4. ***Suitable for administration of drugs which cause gastric irritation***
5. ***For infants & old people who find difficulty in swallowing***
6. ***Administration of drugs which are destroyed by portal circulation***
7. ***Site- specific action on rectal, urethra, etc***

Disadvantages

1. ***Not much acceptable by patient***
2. ***Manufacturing process is difficult***
3. ***Drug which cause irritation to mucous membrane can't be administered***
4. ***Maintenance of temperature is difficult***
5. ***Leakage of suppository occurs upon insertion into the body cavity at elevated temperature***

SUPPOSITORY BASES



- ***As with the ointment bases, suppository base composition plays an important role in both the <u>rate and extent of release of medications.</u>***
- ***Suppository bases may be classified according to their <u>composition and physical properties:</u>***

  <u>1- Oleaginous (fatty) bases</u>

  <u>2- Water soluble or miscible bases</u>

Specifications of suppository bases

1- Origin and chemical composition

The source of origin (i.e. entirely natural or synthetic or modified natural).

Physical and chemical incompatibilities with additives (i.e. preservatives, antioxidants and emulsifiers)

2- Melting range

Since fats do not have sharp melting point, their melting characteristics are expressed as a range indicating the temperature at which the fat start to melt and the temperature at which it is completely melted.

Specifications of suppository bases

3- Solidification point

- ***This value indicates the time required for base solidification when it is chilled in the mold.***
- ***If the interval between the melting range and solidification point is 10ºC or more, the time required for solidification may have to be shortened for a more efficient manufacturing procedure by augmenting refrigeration.***

4- Saponification value

- ***The number of milligrams of potassium hydroxide required to neutralize the free acids and to saponify the esters contained in 1 gm of fat is an indication of the type of glyceride (mono- or tri-) as well as the amount of glyceride present.***

Specifications of suppositories bases

5- Iodine value (iodine index)

- ***This value express the number of grams of iodine that react with 100 gm of fat or other unsaturated material (C=C).***
- ***The possibility of decomposition by moisture, acids, and oxygen (leads to rancidity in fats) increases with high iodine values.***

6- Water number

- ***The amount of water in grams, which can be incorporated in 100 gm of fat at 20 ^{o}C is expressed by this value.***
- ***The water number can be increased by addition of surface active agents.***

Specifications of suppositories bases

7- Acid value

- ***The number of milligrams of potassium hydroxide required to neutralize the free acid in 1 gm of substance is expressed by this value.***
- ***Low acid values or complete absence of acid are important for good suppository bases.***
- ***Free acids complicate formulation work, because they react with other ingredients and can also cause irritation when in contact with mucous membranes.***
- ***Regarding oil-fat rancidity, triglycerides are converted into fatty acids and glycerol causing an increase in acid number***

Properties of an ideal suppository base

- ***Nontoxic and nonirritating** to sensitive and inflamed tissues.*
- ***Inert and compatible** with a broad variety of medicaments.*
- ***No meta-stable forms.***
- ***Can be easily manufactured by compression or molding.***
- ***Dissolve or disintegrate** in the presence of mucous secretions or melt at body temperature to allow for the release of the medication*
- ***Remain molten for a sufficient period** of time to allow pouring into molds.*
- ***Solidify sufficiently rapidly** to minimize sedimentation of dispersed solids.*

Properties of an ideal suppository base

- ***Contract on cooling** to allow easy withdrawal of the suppository from the mold.*
- ***Has wetting and emulsifying properties.***
- ***High water number.***
- ***Stable on storage, does not change color, odor and drug release pattern.***

If the base is fatty, it has the following additional requirements:

- ***Acid value is below 0.2.***
- ***Saponification value ranges from 200 to 245.***
- ***Iodine value is less than 7.***
- ***The interval between melting point and solidification point is small.***

Suppository bases

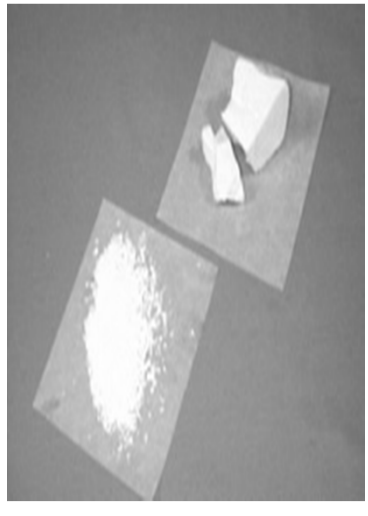
There are two main categories of suppository base:

(1) ***Fatty (oleaginous) bases***

(2) ***water-miscible bases.***

 # A third subcategory may also be used that consists of lipophilic and hydrophilic excipients and therefore shares properties common to both fatty and water-miscible bases.

1. Oleaginous Bases



- ***Fatty bases are predominantly composed of <u>naturally occurring or semisynthetic/synthetic fatty acid esters of glycerol.</u>***
- ***These systems are designed to <u>melt within</u> the rectum there by facilitating drug release and subsequent dissolution***

Include:

- ***Theobroma oil***
- ***Synthetic triglyceride mixtures.***

1. Theobroma oil or Cocoa butter

- ***Theobroma oil or Cocoa butter is used as a suppository base because, in large measure, it fulfills the requirements of an ideal base.***
- ***Cocoa butter is primarily a tri-glyceride, it is yellowish- white, solid, brittle fat, which smells and tastes like chocolate.***
- ***The presence of unsaturated (e.g. oleic acid) esters contributes to the low melting point of cocoa butter (30–36°C), thereby facilitating cocoa butter melting following insertion within the rectum.***
- ***At ordinary room temperatures of 15° to 25°C it is a hard, amorphous solid, but at 30° to 35°C i.e., at body temperature, it melts to a bland, nonirritating oil.***
- ***Thus in warm climates, theobroma oil suppositories should be refrigerated.***
- ***Cocoa butter has iodine value between 34 and 38.***
- ***Its acid value not higher than 4.***

1. Theobroma oil or Cocoa butter

Disadvantages

- ***Shrinks only slightly on solidification; a mold lubricant is therefore required.***
- ***Exists in four polymorphic forms (due to high content of triglycerides) with different melting points (18.9, 23.0, 28.0, and 34.5°C). Theobroma should only be heated for a short time and at temperatures below 36 °C in order to minimize the formation of the unstable low melting point forms***

 # Cocoa butter exists in four polymorphic forms: (1) gamma, melting point circa 18°C, (2) alpha, melting point circa 24°C); (3) beta prime, melting point circa 28°C); and (4) beta, melting point circa 34–35°C).

1. Theobroma oil or Cocoa butter

Disadvantages

- ***When melted and cooled it solidifies in different crystalline forms, depending on the temperature of melting, rate of cooling and the size of the mass.***
- ***If melted at not more than 36°C and slowly cooled it forms stable beta crystals with normal melting point.***
- ***If over-heated then cooled it produce unstable gamma crystals which melt at about 18°C or alpha crystals melting at 23°C.***
- ***Cocoa butter must be slowly melted over a warm water bath to avoid the formation of the unstable crystalline form.***

1. Theobroma oil or Cocoa butter

- ***The change (reduction) in melting point caused by addition of certain drugs such as volatile oils, phenol or chloral hydrate to cocoa butter suppositories. The solution is to raise the melting point back to the desired range by addition of 3% to 5% of beeswax or spermaceti.***
- ***Theobroma oil has a low absorptive capacity for water, but this can be increased by adding surfactants such as cholesterol 2%, emulsifying wax up to 10%, polysorbates 5 to 10%, or wool fat 5 to 10%. However, the addition of surfactants may lead to a drug- base interaction or affect the release of drug from suppository.***

1. Theobroma oil or Cocoa butter

- ***Theobroma oil is prone to oxidation (due to high iodine value); this can be partly overcome by storage in a cool, dark place.***
- ***Theobroma oil may vary in consistency, odor, and color depending on its source like other natural products.***
- ***The low melting point of theobroma oil may pose storage problems in hot climates.***
- ***Don't heat above 34.5 °C for long time Why?***

Need ß seed crystals to get ß form, heat enough to remove a, ß', but keep ß, heat enough ß still present act as seed (don't totally melt before pouring) while, prolonged heating -> no seed crystals (if turns to clear liquid you have problems)

Polymorphic Forms

Polymorphism (Greek: Many - shapes)

- ***Different crystal structures same chemical***
- ***Common example: Diamond and graphite (Both made of Carbon)***
- ***Diamond hardest material while Graphite can't scratch paper, they have different crystal structure, different properties, formulation problem***
- ***One form most stable for given set of conditions***

Example:

- ✓ ***Diamond unstable at room temperature while Graphite more stable at room temp***
- ✓ ***At high temp diamond more stable (diamond metastable form at room temp)***

B- Synthetic Tri-glycerides (hard fat)

- ***The newer synthetic tri-glycerides consist of esterified, hydrogenated or fractionated vegetable oils.***
- ***Their advantages over cocoa butter are:***

1. ***Do not exhibit polymorphism.***
2. ***Contain mainly saturated acids (Iodine number <3), while cocoa butter contains considerable amount of the unsaturated fatty acids (Iodine number 34-38).***
3. ***The melting range of the synthetic bases is usually about 3°C higher than that of cocoa butter***
4. ***The acid content is lower (mostly <0.5)***

B- Synthetic Tri-glycerides (hard fat)

5. ***Hard fat is a mixture of mono, di and tri-glycerides of saturated fatty acids (C_{10} to C_{18}). <u>The hydroxyl value</u> of a base is determined by the proportions of mono and di-glycerides contained in it. A <u>higher hydroxyl value indicates that the base can absorb water more readily and less suitable to easily hydrolyzed drugs.</u>***
6. ***The solidification temperatures of hard fats are unaffected by over heating.***
7. ***There is only a <u>small temperature difference between melting and solidification</u>, thus the sedimentation of suspended drugs is minimized.***

B- Synthetic Tri-glycerides (hard fat)

8. ***Mold lubrication is <u>unnecessary</u> since these bases show <u>marked contraction on cooling</u>.***
9. ***The water absorbing capacity of hard fats can be improved (to about 25% or 30% w/w) by <u>inclusion of glyceryl monostearate</u>.***
10. ***Can be <u>reheated during processing</u> (whilst not affecting the solidification temperature) and exhibit <u>low batch-to-batch variability</u>***

B- Synthetic Tri-glycerides (hard fat)

<u>Disadvantages</u>

- ***More expensive.***
- ***A <u>tendency to fracture</u> upon pouring into chilled molds can be <u>overcome by including very small quantities of polysorbate 80. (avoid refrigeration during preparation)</u>***
- ***On prolonged storage, synthetic suppository bases have been shown to be subjected to <u>crystallization</u>, which causes <u>hardening and increases the melting time</u>. This can be reduced by storage in a cold place.***
- ***<u>The melted fats are less viscous than theobroma</u> oil. As a result greater risk of drug particles to <u>sediment</u> during preparation (lack of uniform drug distribution give localized irritancy)***

B- Synthetic Tri-glycerides (hard fat)

- ***The hard-fat alternatives to theobroma oil are available in various grades with different melting ranges, hydroxyl values and other physicochemical characteristics.***
- ***Some of the bases are single entity formulations.***
- ***Some of the names may denote a series of bases.***
- ***In a series, the bases are varied to give a range of melting points.***

B- Synthetic Tri-glycerides (hard fat)

- ***For example, Fattibase® is a single entity base that consists of triglycerides from palm, palm kernel, and coconut oils.***
- ***Wecobee® is a series of bases. Wecobee FS, M, R, and S are all made from triglycerides of coconut oil. But FS has a melting point range of 39.4 to 40.5°C, M has a range of 33.3 to 36.0°C, R has a range of 33.9 to 35.0°C, and S has a range of 38.0 to 40.5°C.***
- ***Other triglyceride type bases include Dehydag®, Hydrokote®, Suppocire®, and Witepsol®.***

Choice of synthetic/semisynthetic base

Differ in a number of physicochemical properties:

1. ***Hydroxyl number:***

- ***Refers to the presence of hydroxyl groups, which is a measure of the presence of mono- and diglycerides in the suppository base.***
- ***The use of bases exhibiting high hydroxyl numbers should be reserved for therapeutic agents that exhibit low reactivity towards this chemical group.***

2. ***Melting properties:***

- ***Wide range in the melting points, Witepsol H32 exhibit low melting points (31-33°C) and Witepsol E85 (42–44°C)***

Choice of synthetic/semisynthetic base

- ***Low melting bases (37°C) are generally used for the systemic formulation, whereas bases of higher melting points are frequently used in formulations in which a local effect is desired***

3. ***Melting point***

- ***If the active agent is soluble in the base, result in reduction of the melting point (use a suppository base of higher melting point, e.g. Witespol E75 or E85)***
- ***If the drug is more soluble in the base (when heat is applied to melt the base), the drug may precipitate out following cooling.***
- ***This may produce different polymorphic forms of the drug or crystals of a different size fraction (result in a change in the performance of the product).***

Choice of synthetic/semisynthetic base

4. ***Viscosity of the melted base***

Affect the performance of suppositories in two ways:

1. ***During the manufacture: the viscosity of the base will affect both the mixing of the drug with the molten base and the flow of the molten dispersion into the molds.***
   - ***Therefore, in selecting a suppository base, the viscosity of the molten base is a major consideration.***
2. ***The viscosity of the melted base also affects the spreading of the formulation on the rectal mucosa and the subsequent drug release.***
   - ***Bases with high viscosity will exhibit poorer spreading properties and slower rates of drug release when compared to bases of lower melt viscosity.***

Formulation excipients

1. Surface-active agents

- ***These are included to enhance the wetting properties of the suppository base with the rectal fluid.***
- ***This in turn will enhance drug release/dissolution.***
- ***The use of surfactants is mainly reserved for formulations composed of a lipophilic suppository base and/or a lipophilic drug.***
- ***Examples: sorbitan esters and polyoxyethylene sorbitan fatty acid esters***

2. Agents to reduce hygroscopicity

- ***Agents that reduce hygroscopicity, e.g. colloidal silicon dioxide, may be included in fatty suppository bases to reduce the uptake of water from the atmosphere during storage and to enhance the physical and chemical stability***

Formulation excipients

- ***The hygroscopicity of water-soluble or water-miscible bases is large and is indeed partly responsible for the in vivo performance of formulations base***

3. Agents to control the melting point of the base

- ***Examples of excipients used to increase the melting point of suppositories prepared using fatty bases include:***

- ***Beeswax (white or yellow wax)***
- ***Cetyl esters wax USPNF***
- ***Stearic acid***
- ***Atearic alcohol***
- ***Aluminum mono- or distearate***
- ***Colloidal silicon dioxide***
- ***Magnesium stearate***
- ***Bentonite.***

Formulation excipients

- ***Examples of excipients used to reduce the melting point of the fatty suppository base:***
- ***Glyceryl monostearate***
- ***Myristyl alcohol***
- ***Polysorbate 80***
- ***Propylene glycol.***

2. Water Soluble/Water Miscible Bases

- ***Water Soluble/Water Miscible Bases are those containing:***
- ***Glycerinated gelatin***
- ***Polyethylene glycol (PEG) polymers.***

A- Glycerinated Gelatin

- ***Glycerinated Gelatin is a useful suppository base, particularly <u>for vaginal suppositories</u>, where the prolonged <u>localized action is usually desired</u>.***
- ***Glycerinated gelatin suppositories are translucent, resilient, gelatinous solids that tend to <u>dissolve or disperse slowly in mucous secretions to provide prolonged release of active ingredients.</u>***
- ***The commonest is Glycerol Suppositories Base B.P., which has 14% w/w gelatin, and 70% w/w glycerol & water Q.S. to 100%.***
- ***The glycerol-gelatin base U.S.P. consisted of 20% w/w gelatin, and 70% w/w glycerol & water Q.S. to 100%.***

A- Glycerinated Gelatin

- ***It is suitable for use with a wide range of medicaments including alkaloids, boric acid, and zinc oxide.***
- ***Suppositories made with glycerinated gelatin must be kept in well-closed containers in a cool place since they will absorb and dissolve in atmospheric moisture.***

A- Glycerinated Gelatin

Disadvantages:

a- A physiological effect: osmosis occurs during dissolving in the mucous secretions of the rectum, producing a laxative effect.

b- Can cause rectal irritation due to small amount of liquid present.

c- Unpredictable dissolution time.

d- Hygroscopic: so, they should be packaged in tight containers and also have dehydrating effects on the rectal and vaginal mucosa leading to irritation.

e- Microbial contamination likely.

f- Long preparation time.

g- Lubrication of the mold is essential.

A- Glycerinated Gelatin

- ***Suppositories may have a dehydrating effect and be irritating to the tissues upon insertion. The water present in the formula of suppositories minimizes this action and the suppositories may be moistened with water prior to insertion to reduce the tendency of the base to draw water from mucous and to facilitate administration.***
- ***In addition, those suppositories intended for extended shelf-life should have a preservative added, such as methylparaben or propylparaben, or a suitable combination of the two.***

A- Glycerinated Gelatin

Glycerin hygroscopic protect from H_2O

- ***Patient counseling to leave in package***
- ***Will support mold and bacterial growth***
- ***Can use preservative (propylparaben 0.02% & Methylparaben 0.18%)***

Not as good for rectal delivery

- ***Absorb H_2O from mucosal membranes***
- ***Wet before use to:***

1. ***Avoid/reduce "stinging"***
2. ***Faster dissolution***

Preparation of glycerinated gelatin rectal suppositories

- ***Mix or dissolve the medicaments in water to make a total of 10 g.***
- ***Add 70 g of glycerin and mix.***
- ***Add 20 g of granular gelatin, mix carefully to avoid incorporation of air.***
- ***Heat on a steam bath until the gelatin is dissolved.***
- ***Pour the melted mixture into molds and allow to congeal.***
- ***The gelatin constitutes about 20% of the weight of the formula, the glycerin about 70%, and the medicated aqueous portion about 10%.***

B- Polyethylene Glycol Polymers

- ***Polyethylene Glycol Polymers have received much attention as suppository bases in recent years because they possess many desirable properties.***
- ***They are chemically stable, nonirritating, miscible with water and mucous secretions, and can be formulated, either by molding or compression, in a wide range of hardness and melting point.***
- ***Like glycerinated gelatin, they do not melt at body temperature, but dissolve to provide a more prolonged release than theobroma oil.***
- ***Polyethylene glycols are polymers of ethylene oxide and water, prepared to have various chain lengths, molecular weights, and physical states.***
- ***The melting point is often around 50°C.***

B- Polyethylene Glycol Polymers

- ***Certain polyethylene glycol polymers may be used singly as suppository bases but, more commonly, formulas call for compounds of two or more molecular weights mixed in various proportions as needed to yield a finished product of satisfactory hardness and dissolution time.***
- ***The numerical designations refer to the average molecular weights of each of the polymers***
- ***PEGs having average molecular weights of 200, 400 and 600 are clear, colorless liquids while those with molecular weights of 600-1000 are semisolids.***
- ***Those having molecular weights greater than 1000 are wax-like, white solids with hardness increase with increasing the molecular weight.***

B- Polyethylene Glycol Polymers

- ***Since the water miscible suppositories dissolve in body fluids and need not be formulated to melt at body temperature, they can be formulated with much higher melting points.***
- ***This property permits a slower release of medicaments from the base, safe storage at room temperature without need for refrigeration, and ease and slow insertion.***
- ***To prevent irritation of the mucous membranes, they should contain at least 20% of water or dipped in water just prior to use***
- ***Higher proportions of high molecular weight polymers produce preparations which release the drug slowly and are also brittle.***
- ***Less brittle products which release the drug more readily can be prepared by mixing high polymers with medium and low polymers.***

Examples of various PEGs used in suppository bases

1450 8000	30% 70%	300 6000	48% 52%
300 8000	60% 40%	1000 3350	95% 5%
		1000 3350	75% 25%

3. Miscellaneous Bases

- ***Chemical or physical mixtures of oleaginous and water soluble or water miscible materials.***
- ***Emulsions, generally of w/o type (i.e. mixing of cocoa butter with emulsifying agents).***
- ***Polyoxyl 40 stearate is a mixture of the mono-stearate and di-stearate esters of mixed poly-oxyethylene diols and the free glycols.***
- ***Soap may be used as a base (i.e. Glycerin suppositories, USP, with soap as the base).***

Suppositories Compounding

- ***Rx note:***

1. ***Systemic absorption: suppositories prone to erratic absorption (formulation is critical)***
2. ***Local action: not as critical (most bases hold drug in contact with target tissue)***

- ***Base selection:***

1. ***Vehicle influences drug release!***

- ***Cocoa butter immiscible with body fluids***

– Inhibits diffusion of fat-soluble drugs

– Ionized drugs partition more readily

- ***Water-miscible bases***

– Can dissolve very slowly -----> retarding release

Suppositories Compounding

2. ***Systemic absorption***

– Ionized ⇑ bioavailability while non-ionized ⇓ bioavailability (e.g., codeine phosphate or sulfate is better in cocoa butter than codeine)

3. ***Oleaginous vehicles***

– Less irritation of rectum, less popular in vaginal preparations (non absorbable residue)

4. ***Hydrophilic vehicles***

– Less popular rectally (slow dissolution)

– Vehicle ----> relatively slowly cleared vaginally so less likely to leak (where no sphincter muscles)

Suppositories Compounding

5. ***Chemical stability: fatty bases > PEG***
6. ***<u>Some drugs lower melting point:</u> volatile oils, creosote, phenol, chloral hydrate so <u>add white wax or cetyl ester to raises T-melt</u> (note too much wax T-melts > 37 °C)***
7. ***<u>Cocoa butter has no emulsifier:</u>***

- ***Low water uptake 20-30 gm H_2O/100 gm (Tween increases water absorption by 5-10%)***
- ***Hydrophilic drugs can precipitate (Tween helps solubilize hydrophilic drugs)***

8. ***<u>Surfactants:</u>***

- ***⇑ bioavailability (breakup suppository ----> faster release also disperse drug better)***

Methods of Preparation

- ***Suppositories can be extemporaneously prepared by one of three methods.***

<u>1. Hand Rolling</u>

- ***It is the oldest and simplest method of suppository preparation and may be used when only a few suppositories are to be prepared <u>in a cocoa butter base.</u>***
- ***It has the advantage of avoiding the necessity of heating the cocoa butter.***
- ***A plastic-like mass is prepared by triturating grated cocoa butter and active ingredients in a mortar.***

1. Hand Rolling (cont.)

- ***The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile.***
- ***The cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape.***
- ***Effective hand rolling requires considerable practice and skill.***
- ***The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.***

2. Compression Molding

- ***Compression molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mold using suppository making machines.***
- ***The suppository base and the other ingredients are combined by thorough mixing.***
- ***The friction of the process causing the base to soften into a past-like consistency.***
- ***On a small scale, a mortar and pestle may be used (preheated mortar facilitate softening of the base).***

2. Compression Molding (cont.)

- ***On large scale, mechanically operated kneading mixers and a warmed mixing vessel may be applied.***
- ***In the compression machine, the suppository mass is placed into a cylinder which is then closed.***
- ***Pressure is applied from one end to release the mass from the other end into the suppository mold or die.***
- ***When the die is filled with the mass, a movable end plate at the back of the die is removed and when additional pressure is applied to the mass in the cylinder, the formed suppositories are ejected.***

2. Compression Molding (cont.)

- ***The end plate is returned, and the process is repeated until all of the suppository mass has been used.***
- ***The method requires that the capacity of the molds first be determined by compressing a small amount of the base into the dies and weighing the finished suppositories.***
- ***When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients***

3. Fusion Molding

- ***Fusion Molding involves:***

  1- Melting the suppository base

  2- Dispersing or dissolving the drug in the melted base.

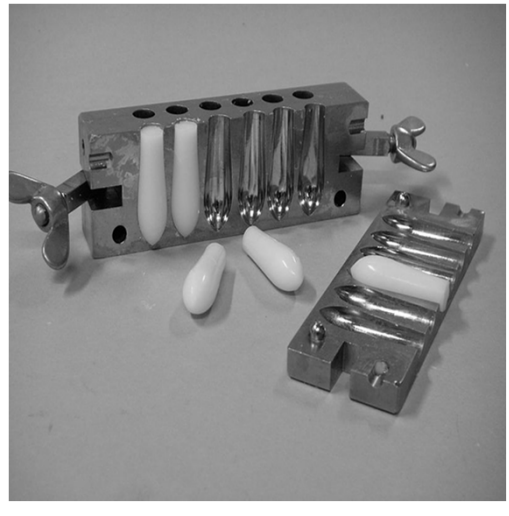
  3- The mixture is removed from the heat and poured into a suppository mold.

  4- Allowing the melt to congeal

  5- Removing the formed suppositories from the mold.

- ***The fusion method can be used with all types of suppositories and must be used with most of them.***

Suppository molds



- ***Small scale molds are capable of producing 6 or 12 suppositories in a single operation.***
- ***Industrial molds produce hundreds of suppositories from a single molding.***

Suppository molds

Lubrication of the mold

- ***Depending on the formulation, suppository molds may require lubrication before the melt is poured to facilitate the clean and easy removal of the molded suppository.***
- ***Lubrication is seldom necessary when the suppository base is contracting sufficiently on cooling.***
- ***Lubrication is usually necessary when glycerinated gelatin suppositories are prepared.***

Base	Lubricant	No lubricant required
• Theobroma oil • Glycerol-gelatin base	• Soap spirit • liquid paraffin	• Synthetic fats • Macrogols

Packaging and storage

- ***Suppositories are usually packed in tin or aluminum, paper or plastic.***
- ***Poorly packed suppositories may give rise to staining, breakage or deformation by melting.***
- ***Both cocoa butter and glycerinated gelatin suppositories stored preferably in a refrigerator.***
- ***Polyethylene glycol suppositories stored at usual room temperature without the requirement of refrigeration***



Testing of suppositories

Finished suppositories are routinely inspected for:

- ***Appearance.***
- ***Content uniformity***
- ***Melting range test***
- ***Drug release test***
- ***Fragility test***
- ***Disintegration test***

Content uniformity

- ***In order to ensure content uniformity, individual suppositories must be analyzed to provide information on dose-to-dose uniformity.***
- ***Testing is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set.***
- ***<u>Assay 10 units individually</u> as directed in the assay in the individual monograph, unless otherwise specified procedure for content uniformity"***
- ***Content uniformity is important <u>not only between suppositories</u>, but also <u>within suppositories</u> in the event that a suppository is halved for administration.***

Dissolution testing

- ***Test for hardening and polymorphic transitions of active ingredients and suppository bases***
- ***Dissolution testing methods include the paddle method, basket method, membrane diffusion method/dialysis method, and the continuous flow/bead method***

Breaking test (Hardness)

- ***To measure the fragility or brittleness of suppository***
- ***Double wall chamber in which the test suppository is placed.***
- ***Water at 37ºC is pumped through the double wall.***
- ***The suppository supports a disc to which rod is attached.***
- ***The other end of the rod consist of another disc to which weights are applied.***

Hardness (cont.)

- ***The test was conducted by placing the suppository to support the axis of 600 g weight.***
- ***At one minute intervals 200 gm weights are added.***
- ***The weight at which the suppository collapses is the breaking point***
- ***When the breaking point reached in the first 20 sec, the added weight was not calculated***
- ***When the breaking point reached in the second 20 sec, half the added weight was calculated***
- ***When the breaking point reached in the third 20 sec, all the added weight was calculated***
- ***Using polyethylene suppositories → H = 1.7 kg.***
- ***Using Glycerin suppositories → H = 1.4 kg.***

Melting range test

- ***Called macro-melting range is a measure of the time it takes for the entire suppository to melt when immersed in a constant-temperature (37°C) water bath.***
- ***USP tablet disintegration apparatus is used***

In-vitro drug release

- ***In-vitro drug release pattern is measured by using the same melting rang apparatus.***
- ***Aliquots of the release medium were taken at different time intervals within the melting period.***
- ***The drug content in the aliquots was determined.***
- ***The drug release pattern was plotted (time versus-drug release curve)***

Factors influencing absorption

- ***Physiologic factors***
- ***Physicochemical factors of the drug and the base:***

  1- Lipid-water solubility of the drug

  2- Particle size of the drug

  3- degree of drug ionization

  4- Nature of the base

1- lipid-water solubility

- ***The lipid water partition coefficient of the drug is an important consideration in the selection of the suppository base and in anticipating drug release from that base.***
- ***A lipophilic drug that is distributed in a fatty suppository base in low concentration has less tendency to escape to the surrounding aqueous fluids than a hydrophilic drug in its saturation concentrations.***
- ***Water-soluble bases dissolve in rectal fluids and release both water-soluble and oil-soluble drugs.***
- ***The more drug in the base, the more dug will be available for potential absorption***
- ***A drug with a high partition coefficient is likely to be absorbed more readily from a water soluble bases.***

2- Degree of ionization

- ***Absorption through rectal mucosa proceeds in accordance with pH-partition theory.***
- ***At the slightly alkaline pH of rectal mucosa, weakly basic drugs will exist in their lipid– soluble unionized form and readily absorbed.***

3- Particle size

- ***For drugs present in the suppository in the un-dissolved form, the size will influence the amount released and dissolved for absorption.***
- ***The smaller the size, the more readily the dissolution of the particle and the greater the chance for rapid absorption.***

4- Nature of the base

- ***If the base interacts with the drug inhibiting its release, drug absorption will be impaired or even prevented.***
- ***If the base is irritating to the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, negating the prospect of thorough drug release and absorption***

- ***The medicament was rubbed into a little of the base (usually on a tile using a spatula) and then stirred into the rest.***
- ***The melted mass was then poured into the relevant mould. Moulds were normally in two parts, made from stainless steel or brass (silver or electroplated to give a smooth surface).***
- ***To facilitate removal the moulds were treated with a lubricant such as oil or soap solution.***
- ***To overcome the difficulty of pouring into the long, thin bougie mould, it was usual to make a larger quantity of base, to partially unscrew the mould, fill with base and then screw the two halves of the mould together thus forcing out the excess***
- ***When cool, any excess base was scraped from the top of the mould, the mould opened and the preparations removed, packed and labelled with the doctor's instructions.***
- ***On a large scale these preparations are made' by cold compression. Cold base is forced into a mould using specially designed machinery.***

Cosmetics

INTRODUCTION

- ***The word cosmetic derives from the Greek Kosm tikos meaning 'having the power, arrange, skilled in decorating'.***
- ***The origin of cosmetics are associated with fighting, hunting, religion and superstition.***
- ***In 3000 BC, early men used cave painting to attract animals for hunting.***
- ***Then they became associated with medicine, and later, as knowledge increased, becoming dissociated from medicine.***
- ***Now, cosmetics is a distinct branch of science with the technologies of its own.***

Toothpastes (Dentifrices)

Requirements for toothpastes

1. ***Should clean the teeth adequately (remove food debris, plaque and stains).***
2. ***It should leave the mouth with a fresh, clean sensation.***
3. ***Low cost to encourage regular and frequent use by all.***
4. ***Harmless, pleasant and convenient to use.***
5. ***Packed economically and stable in storage during its shelf-life.***
6. ***Conform to accepted standards in terms of its abrasivity to enamel and dentine.***
7. ***Claims should be substantiated by properly conducted clinical trials.***

Toothpaste ingredients

- Cleaning and polishing agents (abrasives).
- Surfactant (cleaning and foaming).
- Humectants.
- Binding (gelling) agents.
- Sweetener.
- Flavoring agents.
- Minor ingredients (colors, whitening agents, preservatives).

Toothpaste ingredients (cont.)

- All ingredients have specifications approved for use in foodstuffs

1. Cleaning and polishing agents (abrasives)

1(a) Dental grade silica (SiO_2)n:

- It offers great flexibility to the formulator.
- It can be produced to a high state of purity giving excellent compatibility with therapeutic additives and flavors.
- Varying the particle size can alter the finished product abrasivity.
- Clear gels can be formulated
- Silica can give thickening properties to the dental cream.
- Used in toothpastes, at levels between 10 and 30%.

Toothpaste ingredients (cont.)

1(b) Dicalcium phosphate dihydrate:

- *Most commonly used as it gives good flavor stability.*
- *It is normally white in color (toothpaste does not require additional whitening agents)*
- *It is fully compatible with sodium monofluorophosphate as the fluoride source (formulating with other therapeutic fluoride sources does not appear to have been successful).*
- *Formulated at levels between 40% and 50% to give relatively dense toothpaste.*

Toothpaste ingredients (cont.)

1(c) Calcium carbonate.

- *Most commonly used dental cream abrasives.*
- *Precipitated calcium carbonate (chalk) is available with a white or off-white color.*
- *Precipitated calcium carbonate is incompatible with sodium fluoride, but is stable with the less reactive sodium monofluorophosphate.*
- *Calcium carbonate is used at levels of 30% - 50%.*

Toothpaste ingredients (cont.)

1(d) Sodium bicarbonate (or baking soda).

- Although potentially soluble, it is used primarily as an abrasive ingredient.
- It has a 'salty' mouth-feel (cleaner/deodorizer).
- It is a very mild abrasive, usually used at a 5-30% level, in combination with other abrasives such as silica or calcium carbonate.
- It is used as the sole abrasive agent in some products.

1(e) Other abrasives:

- Hydrated alumina, insoluble sodium metaphosphate and calcium pyrophosphate

Toothpaste ingredients (cont.)

2. Surfactants

- Aid in the penetration of the surface film on the tooth by lowering the surface tension.
- Providing foam to suspend and remove the debris.
- Surface-active agents chosen for use in dentifrices are non-toxic and non-irritant to the oral mucosa under normal usage conditions.
- Soaps used as surfactant, was incompatible with some other components of the paste and have an unpleasant odor and a bitter taste.

Toothpaste ingredients (cont.)

- *Synthetic materials are preferred, have better foaming properties, more compatible with other ingredients since their pH range is neutral, higher degree of purity that can eliminate some of the bitter flavor components that affect taste.*
- *Surfactants are used at a concentration of around 1-2% by weight in the dental cream.*

Sodium lauryl sulphate (SLS)

- *The surfactant of choice, used in nearly all toothpaste brands across the globe.*

Toothpaste ingredients (cont.)

3. Humectants

- *Humectants are used to prevent the paste from drying out and hardening.*
- *Give shine and some plasticity to the paste.*
- *Two major humectants are used in toothpaste*

3(a) Glycerin:

- *The best humectants, producing a shiny, glossy product.*
- *Stable, non-toxic, available from both synthetic and natural sources, and provides a useful sweetening function to the paste.*

3(b) Sorbitol:

- *Sorbitol syrup (approximately 70%) is used throughout the industry and is sometimes considered superior to glycerin depending upon the formulation.*
- *It also imparts sweetness, and is a stable humectant.*

Toothpaste ingredients (cont.)

3(c) Propylene glycol and polyethylene glycol:

- ***More expensive.***
- *They are used in combination with either glycerin or sorbitol.*

3(d) Xylitol.

- ***Like sorbitol its sweetness equal to sugar.***
- *Its current use in toothpaste is to augment the anti-caries effect of fluoride.*
- ***Its high cost and limited availability restrict its use.***

 # The total humectant loading is in the range 10-30% by weight

Toothpaste ingredients (cont.)

4. Gelling agents

- *Hydrophilic colloids which disperse and swell in the water phase of the toothpaste and maintain the stability of the paste.*
- *Can influence the dispersibility of the paste in the mouth, the generation of foam and, the release of the flavor components.*

Sodium carboxymethyl cellulose CMC.

- ***Manufactured to a high state of purity, give flexibility in terms of solubility, elasticity with increased stability in the presence of electrolytes.***

 # Other gelling agents include: Carrageenan, Xanthan, Hydroxy-ethyl cellulose and Clays - colloidal clays

- *Added to a paste from 0.5% to 2.0% by weight.*

Toothpaste ingredients (cont.)

- ***5. Sweetening agents***
- ***These are important for product acceptance, since the final product must be neither too sweet nor too bitter. E.g. Sodium saccharin (used at a level between 0.05% and 0.5% by weight).***
- ***6. Flavors***
- ***Flavors are probably the most crucial part of toothpaste since the primary consumer requirements of toothpaste is the perception of freshness and cleanliness after brushing (mint flavors tend to predominate).***
- ***Thymol, anethole, menthol give a pleasant cooling effect.***
- ***Eugenol (clove oil), cinnamon, eucalyptol, aniseed, and wintergreen give a medicinal effect.***
- ***# The flavor level may vary from around 0.5% to 1.5% by weight.***

Toothpaste ingredients (cont.)

Minor ingredients

(a) Titanium dioxide: give additional whiteness and brilliance to the paste.

(b) Colors: influence consumer preference.

A small amount is necessary, <0.01% by weight.

(c) pH regulators:

(d) Sparkles: gives toothpaste the appearance of containing 'sparkles' and is especially aimed at younger children.

Micro-granules are silica agglomerates of different particle size than normal abrasive or thickening silica. (supporting the consumer advertising)

Toothpaste ingredients (cont.)

Fluoride and other 'active' ingredients

- ***Inclusion of this type of ingredient pushes the toothpaste industry into a borderline classification area somewhat beyond the simple definition of a 'cosmetic'. Thus the ingredient, level, formulation and claimed therapeutic benefit to the consumer need to be reviewed together.***

Manufacture of toothpastes

Method 1

- ***Blend all powder components together, including the gelling agents, abrasives and thickening agents.***
- ***Blend this mix with all the aqueous and liquid components of the paste (humectants, water) in a heavy-duty mixer (until complete swelling of the gelling agents).***

Method 2

- ***The gelling agent is fully hydrated in the presence of sufficient water and heat if necessary.***
- ***All soluble salts may be added***
- ***Mix the fully dispersed gel and the powders together also in a heavy-duty mixer***

Manufacture of toothpastes

Addition of flavor and surfactants

- *To the paste obtained from either process mix with both the surfactant and the flavor under vacuum (to de-aerate the product otherwise 'mousse'-type consistency will be produced).*
- *These are often added as late as possible as mixing the surface-active agent will create foaming and air entrapment.*
- *Equally mixing under vacuum with the flavor added could cause loss of some flavor components that can be up to 25% of the total raw material cost of the toothpaste*

Toothpaste Formulations

I. *Anti-cavity (fluoride)*
II. *Anti-tartar toothpastes*
III. *Toothpaste for the control of plaque and gingivitis*
IV. *Toothpaste offering whitening or sensory signals*
V. *Toothpastes for sensitivity*

Anti-cavity (fluoride)

- *People living in areas with naturally fluoridated water (optimal < 1 ppm), had significantly lower levels of dental caries compared to those living in a non-fluoridated region*
- *The maximum level permitted is 1500 ppm F~.*

Fluoride sources

- *Sodium monofluorophosphate*
- *Sodium fluoride (NaF)*
- *Organo (amine) fluorides*
- *Stannous fluoride (SnF)*

Anti-cavity (fluoride)

- ***Fluoride must be in a soluble state.***
- *It is not effective if it is bound to the abrasive: when free flouride ions are present in a calcium carbonate formula insoluble calcium fluoride will precipitate losing its action .*
- *Sodium monofluorophosphate would be chosen as the fluoride source since the fluoride is present in a protected form (this requires the monofluorophosphate to be hydrolyzed in the mouth)*
- *Xylitol, a non-fermentable polyol, may be formulated as NaF/silica/10.0% xylitol to provide significant reduction in dental caries, when compared to a positive control product containing NaF/silica alone (but this formula is of high cost)*

Anti-cavity (fluoride)

- *The efficacy of fluoride (F ~) may be enhanced if it is combined with the calcium ion (Ca^{2+}) at the moment of brushing.*
- *Dual-chamber packaging is utilized and the basic dentifrice ingredients are separated until the moment of brushing, thus minimizing any potential reactions.*
- *Fluorosis is a side effect of chronic fluoride overdose during the pre-eruptive stages of tooth development resulting in a continuum of signs varying from fine white opaque lines to chalky white teeth.*

Anti-tartar toothpastes

- *Once tartar is formed, it is not removed by brushing (because of its chemical similarity to the tooth mineral)*
- *Inhibiting tartar crystals growth processes is achieved by adding pyrophosphate ions. These have been introduced in various forms:*
  - *Tetra-sodium pyrophosphate (TSPP)*
  - *Tetra-potassium pyrophosphate (TKPP)*
  - *Disodium dihydrogen pyrophosphate*
  - *Addition of 1.5% of an organic copolymer Gantrez® to the 1.3% pyrophosphate ion will protect the pyrophosphate in the mouth enhancing its effectiveness, and give a better taste*

Toothpaste for the control of plaque and gingivitis

- *Compounds with anti-microbial properties that can retard plaque formation and prevent gingivitis*
- *It should retained in the oral environment for long time after the short brushing period.*
- *Chlorhexidene: is a broad-spectrum anti-bacterial agent bound and retained in the mouth for several hours but it cause staining of the teeth, increased calculus formation, and taste alteration*
- *Triclosan: does not have a high affinity for the oral tissues (addition of the organic co-polymer Gantrez® has increased the retention of triclosan in the oral environment for long periods of time)*

Toothpaste offering whitening or sensory signals

- *Peroxide has been added for whitening purposes, it is used at a low level, 0.1-0.5 % active oxygen either in the from of hydrogen peroxide (H_2O_2) or as calcium peroxide (CaO_2).*
- *The main purpose of its introduction into toothpaste has been to impart a credibility to products positioned as 'whitening' products*
- *Introduction of dual-chamber packaging (allow peroxide to be kept separate until they were delivered to the brush)*
- *Baking soda and peroxide products delivered as a single tube (to avoid the cost of the complex dispenser packaging), they are anhydrous dentifrice to avoid interactions.*

Toothpastes for sensitivity

- ***Dentifrices have a beneficial effect on sensitive teeth (painful responses to hot and cold stimulation of the teeth).***
- ***The most commonly used ingredients: Strontium chloride, Strontium acetate, Formaldehyde and Hydroxyapatite***
- ***# Soluble potassium ions as a desensitizing preparation became more prevalent (the soluble potassium ion can penetrate the open dentine tubules to reach the nerve fibers at the base, where it can exert a depolarizing and thus desensitizing effect.***
- ***Ingredients used in these type of dental creams typically are: Potassium nitrate, Potassium chloride, and Potassium citrate***

Mesotherapy

Mesotherapy

- *Used to treat a broad spectrum of medical disorders such as allergies, arthritis, asthma, depression, fibromyalgia, irritable bowel syndrome, immune system deficiencies, and insomnia.*
- *Has dermatologic uses such as acne, hair loss, various types of dermatitis, scars, chronic itching, psoriasis, stretch marks, spider veins, venous insufficiency, and vitiligo.*
- *The cosmetic uses include aesthetic medicine to treat photo-aging. Tightening of loose, saggy skin on the face and neck, reducing the extent of wrinkling.*
- *Mesotherapy is also used to treat pigmentary changes.*

Mesotherapy

- *Treatment employing minute doses of multiple pharmaceutical medications, natural plant extracts, vitamins, amino acids, and other ingredients, which are injected into various levels of the skin depending on the indication of treatment.*
- *Mesotherapy may be injected subcutaneously (into the fat layer just beneath the skin) to treat localized adiposity, whereas for skin rejuvenation, the injection is targeted into the dermis.*
- *Mesotherapy is based on a simple principle: to inject little , and at the right place (a medicinal "bullet" is delivered directly to a particular target area in the body)*

Techniques of Mesotherapy

- **Depend on the target area to be treated including intra-epidermal (tremor), superficial intradermic (multipricking), deep intra-dermic (point per point), and intra-hypodermic..**

1. Intra-epidermal (Tremor):

- Injecting the mesotherapeutic agents into the epidermis.
- The term "tremor," regarding this technique, refers to the rapid fine movements of the injection.
- A tuberculin syringe with a 4-mm needle, or a mesogun is used to inject the medications into the epidermis.

Techniques of Mesotherapy

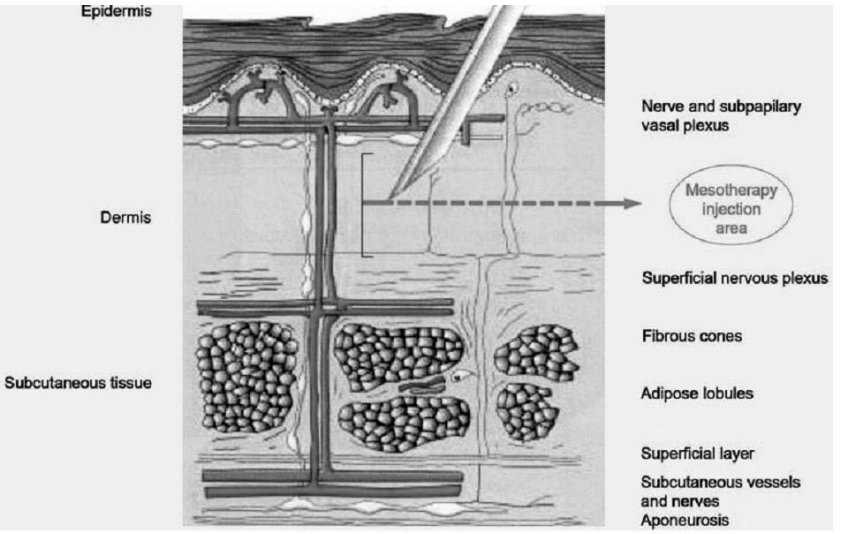
- It is intended for facial rejuvenation.
- Mesotherapy injections at two-week intervals for a total of 10 treatments is advised.
- The success of the treatment depends on the accuracy and technical skills of the administering physician in the use of either the mesotherapy gun or the syringe.

Techniques Of Mesotherapy

2. Superficial Intradermic (Multipricking)

- ***Refer to the injection of mesotherapeutic agents into the dermis by multiple rapid injections delivered using a 4- or 6-mm needle.***
- ***Injections should produce a wheal—which is a rounded- or flat-topped, pale-red papule or plaque that is characteristically evanescent, disappearing within hours***
- ***Used for injections in the treatment of cellulite.***
- ***Mesotherapy injections weekly for 10 to 15 visits is advised.***
- ***The number of treatment sessions depends on the patient response and may be tapered off to once a month for maintenance.***

Techniques Of Mesotherapy



Techniques of Mesotherapy

3. Deep Intradermic (Point Per Point)

- *Employed for arthritis and tendonitis where medicines are injected into the dermis using a 4-mm needle.*
- *Injections are directed to the areas that are inflamed or affected by disease.*
- *Patients may benefit more from immediate relief of pain and inflammation than taking oral medications.*

4. Intra-Hypodermic

- *Injections into the hypodermis or subcutaneous layer of the skin are used for lower back pain or musculoskeletal pain.*
- *Needle length of 13 mm is used to deliver mesotherapeutic cocktails.*

MESOLIFT

- *As one ages, the blood supply to the skin decreases, resulting in a reduction in the flow of oxygen and nutrients to tissues.*
- *Free radicals cannot be eliminated from the bodily tissues as easily as in the young.*
- *Mesolift is a mesotherapy procedure that helps minimize wrinkles and improves skin elasticity and tone and texture.*
- *It enhances skin contour, lifts sagging skin in the areas of the face and neck, and decreases wrinkles and "crepe" skin in the facial and d´ecollet´e areas (it can give one a fresher and healthier look, defying the aging process).*

MESOLIFT

- *The mesolift products may contain hyaluronic acid, highly concentrated vitamins, trace elements, coenzymes, amino acids, and antioxidants that nourish and rejuvenate the skin, promoting the production of collagen and elastin, and stimulation of metabolism.*
- ***They also improve circulation in the small blood vessels of the skin, strengthening its structure and restoring its firmness.***

Hyaluronic Acid + Vitamin C + Vitamin A Cocktail	
Hyaluronic acid 3.5 %	*Amino methyl silanetriol, vitamine C , procaine, Vitamin A*

Mesolipotherapy

- ***It offers an alternative to liposuction and is regarded as a safe treatment of localized areas of adiposity.***
- *Mesolipotherapy removes fat from adipose tissue without completely destroying it.*
- ***The most commonly used agent in mesolipotherapy is phosphatidylcholine which is a lipolytic substance that initially increases the blood flow in the affected area, causing local breakdown of fat.***

Hair Removal

Hair Removal

Epilation:

- *Hair is removed by its root.*
- *Depending on the particular type of epilation method, the hair may be eliminated temporarily or permanently.*
- *Electrolysis is a method of epilation that aims to eliminate hair permanently on the other hand, plucking the hair (using wax or a thread) is a method of epilation where the hair is only removed temporarily.*

Depilation:

- *Hair removal that does not involve the root of the hair, but a region higher up the hair shaft, or at near the surface of the skin.*
- *Examples of depilation are shaving and the use of depilatory creams. (All depilation methods remove hair only temporarily)*

Chemical Depilatories

- *Marketed as creams or ointments, but some are also available as gels or foams or in a roll-on form.*
- *Contain chemical substances that dissolve the keratin fibers (from which the external part of the hair is made).*
- *The hair comes off at or just below skin level.*
- *The hairs tend to break in those places where the keratin is slightly deficient or unevenly distributed.*
- *Chemical depilatories affect only the external part of the hair and not the living root.*
- *Therefore, within a few days, the hairs growing back can be noticed.*

Chemical Depilatories

Main Types of Preparations

1. Sulfides:

- *Barium sulfide and strontium sulfide.*
- *When using these substances, hydrogen sulfide gas (H_2S) is formed, which has a repulsive "rotten egg" smell and irritates the skin.*

2. Thioglycolates

- *The main component of the preparations currently used.*
- *The basic ingredient of depilatory agents is a salt of thioglycolic acid.*
- *These compounds act on the fibers of the hair, dissolving and disrupting the keratin.*

Chemical Depilatories

Thioglycolates:

- ***Less irritant** than sulfides, have **less offensive odor** compared with sulfides.*
- *It takes longer for the hair to come away from the skin.*
- *Because thioglycolates **rarely cause skin irritation**, they are designed for use on areas of sensitive skin, such as the face.*
- *The length of application time is determined by the manufacturer, and is usually between 5 and 20 minutes, depending on the nature of the preparation and the strength of the hair.*
- *These preparations work well on fine hair*

Chemical Depilatories

3. Enzymatic Depilatory Agents

- *There is **no problem of odor or skin irritation** with enzymatic depilatory substances.*
- *The basic component is **an enzyme called keratinase**, which dissolves the protein of the keratin that makes up the hair.*
- *The enzyme is produced by certain bacteria.*
- *These compounds are **less effective than sulfides and thioglycolates***

Chemical Depilatories

Disadvantages of Depilatory Agents

- *There may be skin irritation.*
- ***Chemical depilatories may affect not only the hairs but also the superficial layers of the skin (both the hair and the skin are composed of keratin).***
- *Mild irritation may be treated by 1% hydrocortisone cream or aloe vera preparations.*
- *They can give rise to an unpleasant odor.*
- ***Regrowth of the hair can occur following the use of a depilatory agent (although the hair is removed at a deeper level than with shaving)***

Permanent Hair Removal: Electrolysis

- *Electrolysis is an effective method for the permanent removal of hair, based on inserting a fine metal needle into the hair follicle, with the aim of destroying the active cells in the hair root.*
- *Hair follicle is an elongated, tube-like depression, in which a hair grows. at the base of the follicle are the active cells of the hair root, responsible for its growth.*
- *To destroy these active cells, a fine metal needle is inserted through the opening of the follicle and advanced until the tip reaches the base of the follicle.*
- ***At this stage, an electric current is passed down the needle to destroy the active cells at the hair root.***

Hair Removal Using Lasers

- ***Several types of laser devices are used for this purpose: alexandrite, diode, and Nd:YAG.***
- ***The type of laser used should be adapted <u>according to the color of the skin and the area to be treated.</u>***
- ***The principle on which this treatment is based is that there is a <u>difference in color between the hair follicle and the skin</u>; the light energy is absorbed by the dark pigment in the hair follicle causing damage to the follicle, thereby reducing hair growth.***
- ***<u>The lighter the skin and the darker the hair</u>, the more selectively the laser will affect the follicle and not the surrounding tissue.***

Hair Removal Using Lasers

<u>The main side effects of this treatment are:</u>

1. ***Mild discomfort during treatment (may require local anesthetic)***
2. ***Local redness, which may last from a few minutes to a few hours.***
3. ***Superficial burns, usually resolving without leaving any residual sign.***

 # Laser treatment for hair removal in people with dark skin is not desirable because there is insufficient difference between the color of the hair and the color of the skin

Hair Removal Using Lasers

- ***Laser treatment arrests the active growth period of the treated hair for several years.***
- ***The response varies according to the region of the body being treated, skin type, and the age of patient.***
- ***For instance, the hair in the armpits, groin, and legs is more responsive to laser treatment than facial hair.***
- ***The response to the treatment may also vary considerably from person to person.***
- ***Hair that has not reappeared within a year after treatment is not expected to regrow.***
- ***Laser treatment before adolescence would not be effective enough***

Chemical Skin Peeling

Chemical Skin Peeling

- *Chemical skin peeling is a method of peeling the outer layers of the skin by creating a chemical burn.*
- *As the burn heals, a new outer layer of skin forms.*
- *The new skin that appears is smoother, pinker, and has a more uniform texture.*
- *After chemical peeling, sun spots (solar lentigines) on the skin become paler, wrinkles are smoothed out to a certain extent, and even disappear completely.*

Chemical Skin Peeling

Peeling Agents

1. *"dry ice" (carbon dioxide snow)*
2. *Jessner's solution, which contains resorcinol, salicylic acid, and lactic acid*
3. *α-hydroxy acids*
4. *Trichloroacetic acid (TCA).*
5. *Phenol.*

- *Selection of peeling agent depend on the depth of peeling to be achieved, the patient's skin type*

Chemical Skin Peeling

- ***Chemical skin peeling can be performed to <u>four different depths of penetration</u>, each intended to achieve a different end result. These are as follows:***

1. ***<u>Very superficial peeling:</u> which involves only the epidermis. there may be minimal involvement of the dermis.***
2. ***<u>Superficial peeling:</u> which includes the epidermis and the outermost part of the dermis.***
3. ***<u>Medium peeling:</u> which reaches the dermis deeper than superficial peeling.***
4. ***<u>Deep peeling:</u> which reaches deeper into the dermis, to approximately half its depth.***

Chemical Skin Peeling

<u>Preparations Used in Chemical Skin Peeling</u>

- ***<u>Very superficial peeling:</u> may be performed using 10% to 20% trichloroacetic acid, Jessner's solution, or α-hydroxy acids.***
- ***<u>Superficial peeling:</u> may be performed using 35% trichloroacetic acid or 50% to 70% α -hydroxy acids.***
- ***<u>Medium peeling:</u> may be carried out using 35% trichloroacetic acid combined with dry ice or with Jessner's solution.***
- ***<u>Deep peeling:</u> usually utilizes phenol.***

Chemical Skin Peeling

• ***Complications:***

1. ***Bacterial infection***
2. ***Alteration in skin pigmentation***
3. ***Scarring***
4. ***Herpes virus infection in the peeled area***
5. ***Sensitivity to cold***
6. ***Prolonged redness***
7. ***Heart and kidney problems***
8. ***Effect of sun light***

Antiperspirants and Deodorants

Antiperspirants and deodorants

- *Available as creams, powders, sticks, squeeze bottles, roll-ons, aerosols, pump sprays, suspension solids, suspension roll-ons, soft solids and gels*

1. *Antiperspirant:*

- ***Reduces the amount of perspiration.***
- ***In the USA, an antiperspirant is classified as an over-the-counter (OTC) drug.***
- ***In the UK, an antiperspirant comes within the definition of a drug, in that it has a physiological action.***

Antiperspirants and deodorants

2. *Deodorant:*

Masks and/or reduces axillary odor through the use of an antimicrobial agent or a fragrance.

- *Deodorants have a non-therapeutic effect and are regarded as cosmetics, not subject to regulatory control in the UK or in the USA.*
- ***It should be noted that a 'deodorant' is not an 'antiperspirant', but an 'antiperspirant' is automatically a 'deodorant'. (aluminium salts have bactericidal properties).***
- *Accordingly, the labels of antiperspirants display the dual description 'antiperspirant/deodorant'.*

Antiperspirants

Mechanism of action:

- ***Diffusion of the soluble antiperspirant active ingredient into the sweat duct coupled with the slow neutralization of the acidic metal salt.***
- ***This produces a gelatinous and insoluble polymeric aluminum hydroxide-protein gel which acts as a partial obstruction at the orifice of the sweat gland so reducing, but not stopping, the flow of axillary perspiration.***

Antiperspirant active ingredients:

- ***Including water-soluble aluminium complexes as Aluminum Chlorohydrate, Aluminum Sesquichlorohydrate, Aluminum Chlorohydrex, Aluminum Zirconium Trichlorohydrate, and Aluminum Zirconium Tetrachlorohydrate***

Deodorants

- ***Deodorants, reduce underarm odor by exerting an antibacterial action on the organisms which decompose apocrine axillary secretions.***
- ***The earliest formulations were based on zinc oxide, boric acid and, later, benzethonium chloride.***
- ***Hexachlorophene increasingly replaced all other bactericides and was used successfully until it was replaced by triclosan and zinc phenolsulfonate.***
- ***The most popular product forms of deodorants are sticks and aerosols, with the active ingredient dissolved in alcohol.***

Deodorant properties of ACH and AZCH

- ***ACH was first introduced as an antiperspirant.***
- ***Aluminum chlorohydrate, chloride and sulphate are effective in preventing growth of microorganisms on hydrated skin.***
- ***The principal deodorancy effect of antiperspirants is a result of antibacterial actions.***
- ***Low concentrations of aluminum chlorohydrate and aluminum zirconium chlorohydrate, i.e. 4% and 6%, respectively, result in faster antimicrobial kill rates of the organisms responsible for axillary odor, than do relatively high levels of triclosan***
- ***These products are marketed as dry deodorants with full deodorant effectiveness and mild antiperspirant effect.***

Formulations

a) Creams:

- ***One of the first products that are oil-in-water emulsions (required acid-stable emulsifying agents).***
- ***To be applied with their fingers to the axillae .***

b) Sticks and solids:

- ***Typically based on sodium stearate as the gelling agent (either propylene glycol or alcohol).***
- ***They also contain an anti-microbial agent, humectant and perfume.***
- ***These formulations are aesthetically pleasant and have excellent application characteristics, but the antiperspirant efficiency is low.***

c) ROLL-ONS:

- ***One of the most popular carrier forms of antiperspirant.***
- ***There are several types of roll-ons depending upon their formulation base. For e.g.***

Formulations

1. ***Water, alcohol, hydro-alcoholic systems, esters and silicones.***
2. ***Water-based roll-on (o/w)- usually an oil-in-water emulsion. They show an excellent physical stability and ease of application.***

Water-based roll-on Alcohol-based roll-on

- ***Alcohol-based and hydro-alcoholic roll-ons- they allow a shorter drying time.***
- ***Only actives with adequate alcohol solubility works in this system (e.g. alcohol soluble ACH, aluminium zirconium pentachlorohydrate).***
- ***Clear water-in-oil roll-ons- These are relatively new on the market.***
- ***They demonstrate superior aesthetics and leave no residue or deposit on the skin after application.***

Formulations

d) AEROSOLS

- ***These are the most widely used products till date.***
- ***The main advantage of this system is it doesn't involve the container or the product coming in contact with the skin of the user.***
- ***Usually in these preparations, enhanced efficiency aluminium chlorohydrate is used as active.***
- ***A hydrocarbon propellant system is included in the formulation.***

Evaluation of Deodorants

- ***Both in vivo and in vitro methods are available. But In vitro techniques do not provide a reliable indicator of clinical effectiveness.***
- ***The two principal methods for the in vivo evaluation of deodorant efficacy are-***

1. Determination of the effect of treatment on the skin microflora:

The axillary skin is tested for quantifying the microflora present in it

2. Olfactory assessment of the effects on skin odors:

Olfactory assessment of the effect of deodorants on body odors may be performed by direct armpit sniffing or by indirect sniffing of pads.

Antiperspirants evaluation

- ***Antiperspirants aim to bring about a temporary decrease in sweat production in the axillae.***
- ***The most widely used procedure for efficacy testing of antiperspirants is a gravimetric method which involves the collection and weighing of axillary sweat under controlled conditions.***
- ***The percentage of reduction is calculated***

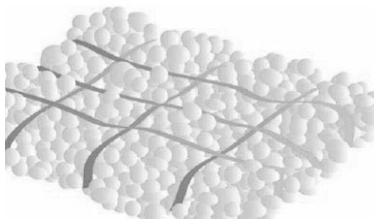
Cellulite

Cellulite

- *Refers to an unsightly distribution of fat under the skin, in certain areas of the body—especially the thighs and buttocks.*
- ***The subcutaneous fat is distributed in a manner that creates hollows and bumps in these areas.***
- *Cellulite is much more common in women than in men, affecting 80% to 90%, especially older than 35 years.*
- ***It may be related to hormonal factors***
- *Under the dermis lies a layer of fat, called the subcutis. this layer is made up of many fat cells that coalesce to form fatty tissue.*
- ***These lumps of fat are surrounded and separated from each other by rigid strands***

Cellulite

- *If there is a high dietary intake of fats or carbohydrates (which are converted to fat in the body), the fat cells fill up with fat, swell up, and may grow to three or more times their normal size.*
- *At the same time, the rigid strands cannot stretch beyond a certain amount. Thus, the fatty tissue bulges out from the strands around it*



Cosmetic preparation for cellulite

- *Penetrate through the keratin layer, the epidermis, and the dermis and "dissolve" the excess fatty tissue.*
- *The active ingredients commonly present in these preparations are methylxanthines, various plant extracts, and vitamin A derivates.*
- *Some of these compounds have been combined with liposome technology, that may assist in deeper penetration of the active ingredients into the skin.*

1. *Plant Extracts: contain substances similar in their chemical structure to the methylxanthines.*
2. *Retinoids and Vitamin A Derivates: topical agents are used as for cellulite.*

Cosmetic preparation for cellulite

3. Methylxanthines:

They break down and dissolve the fat in the cells.

Substances in this group include:

- ***Theophylline, (derived from tea leaves, or produced synthetically), caffeine, (present in coffee, tea, cola), and aminophylline, used as a medication in asthma.***
- ***Application onto the skin, penetrate the subcutaneous tissues, dissolve the fat, and improve the texture of the tissues.***
- ***Or it may reduce the amount of water between fat cells.***
- ***This may give the impression of firmer tone in that area.***

Astringents

Astringents

- *Used to give the skin a cool, refreshing feeling, to temporarily constrict the skin pores and to remove the outer layer of oil from the skin.*
- *Called "skin tonics," or "skin toners."*
- *Used as solutions, or gels to be applied following skin cleansing*
- *Used before a moisturizer or liquid foundation make-up is applied.*
- *The commonest form is aftershave products.*
- *Astringents are solutions containing a mixture of alcohol and water in various proportions (such as menthol or camphor)*

Astringents

- *Astringents for use on dry skin should contain minimal concentrations of alcohol alc tends to dry out the skin).*
- *For very dry skin, astringent-containing moisturizers should be used.*
- *On the other hand, astringents for use on oily skin have a higher concentration of alcohol.*
- *The active component of these products is astringent. Denatured ethanol (5-25%.) is commonly used as the astringent material.*
- *Astringent lotions- are useful in the control of very oily or acne-prone skin. These products often contain high levels of ethanol and sometimes isopropanol .*

Astringents

- *Astringents usually contain aluminum or zinc salts, which are said to constrict the pores. So prevent the entry of dirt, particles of soot and dust into the pores.*
- *Alcohol also gives a feeling of coolness because of its rapid evaporation from the skin.*
- *The solutions may also contain dyes and fragrances.*
- *Witch hazel extract, for example, is derived from the leaves of the Hamamelis virginiana tree has anti-inflammatory properties (it is a common ingredient in astringents and aftershave preparations)*

After-shave products

- *This products are used to- Alleviate after-shave skin trauma, to cool and refresh skin, exert mild astringent effect.*

AFTER-SHAVE LOTION

- *Most popular type product, containing about 40-50% of ethanol and the appropriate level of water.*
- *The ethanol/water ratio may be adjusted depending on the type and level of perfume.*
- *In some instances it is necessary to use a perfume solubilizer .*
- *Other ingredients include: propylene glycol as humectants; menthol as cooling agent; witch hazel as astringent, quaternary ammonium compounds as biocides , and di -isopropyl adipate as emollient.*

After-shave products

AFTER-SHAVE GEL GELS:

- ***Are made by using a combination of a carboxyvinyl polymer (A) and a base (B).***
- ***The stiffness of the gel can be altered by varying the amount of the polymer and the triethanolamine addition***

Cosmetic Use Of Botulinum Toxin

Cosmetic Use of Botulinum Toxin

- ***Botulinum toxin (BTX) is a neurotoxin that is used in the treatment of wrinkles and facial rejuvenation.***
- ***When injected in small quantities, it reduces the power of the target muscles, reducing the wrinkles associated with those muscles for a period of four to six months***
- ***BTX is naturally produced by the bacterium Clostridium botulinum (cause food poisoning-induced muscle paralysis botulism).***
- ***BTX has been used for certain neuromuscular disorders, such as involuntary muscle spasm and strabismus ("cross-eyes").***
- ***Used to treat migraine and hyperhidrosis (excess sweating).***

Cosmetic Use of Botulinum Toxin

- ***BTX blocks the release of the neurotransmitter, acetylcholine leading to muscle contraction.***
- ***Only five serotypes (has seven) affect the human nervous system, BTX-A,B,E,F,G, and only two of these are available as medicines, BTX-A and BTX-B***

Dynamic Wrinkles

- ***Dynamic wrinkles and expression lines gradually develop over the years due to repeated contraction of the facial muscles.***
- ***These can be treated by BTX (the muscles of the face are attached to the skin).***
- ***With aging, these dynamic wrinkles evolve into resting wrinkles that become permanent and gradually deepen.***

Cosmetic Use of Botulinum Toxin

- *It is important to select patients in whom the negative facial signs are caused by an underlying muscle pull.*
- *Patients with advanced or severe photoaging, who have many wrinkles at rest, are not good candidates.*
- *The common indications for BTX-A lie in the upper face including glabellar lines (the vertical lines between the eyebrows), forehead wrinkles, and crow's feet (wrinkles at the outer edges of the eyes).*
- *Less common indications are in the mid and lower face and include lip wrinkles, marionette lines, cobblestoning of the chin, and facial asymmetries.*
- *BXT products: Botox® and Dysport® share the majority of the aesthetics market*

Cosmetic Use of Botulinum Toxin

- *The clinical effect of BTX begins to be apparent at 48 hours, reaches its maximum after one to two weeks and lasts for four to six months.*
- *The treatment should then be repeated to maintain the desired result*
- *# The effect is temporary and that further treatment will be necessary after three to six months*
- *Many fear the "frozen" look that with higher BTX dosing*
- *BTX-A treatment is contraindicated in the presence of neuromuscular diseases that could amplify its effect.*
- *BTX should not be used during pregnancy and lactation.*