Topical and Suppository Forms

01. Cutaneous Forms (Applied to the Skin)

These forms allow the medication to be applied to the skin. It can either act locally or penetrate the skin and pass into the bloodstream. The main forms for cutaneous application are ointments (greasy preparations), creams (less greasy), gels (non-greasy, clear), solutions, and powders.

a. Ointment:

1. Hydrophobic Ointments: Hydrophobic (lipophilic) ointments can normally only absorb small amounts of water. The most commonly used substances for formulation are petrolatum, paraffin, liquid paraffin, vegetable oils or animal fats, synthetic glycerides, and waxes.

2. Water-absorbing ointments: These ointments can absorb larger quantities of water. Their excipients are those of hydrophobic ointments, incorporating (W/O) type emulsifiers: sorbitan esters, wool fats, monoglycerides, fatty alcohols, etc.

3. Hydrophilic ointments: Hydrophilic ointments are preparations whose excipients are miscible with water. They are usually composed of mixtures of liquid and solid polyethylene glycols (PEGs). They can contain very large quantities of water.

b. Creams: These are multiphase preparations:

• Hydrophobic creams: W/O emulsions (wool fat, sorbitan esters, monoglycerides)
• Hydrophilic creams: W/O emulsions (sodium soap, sulfated fatty alcohols)

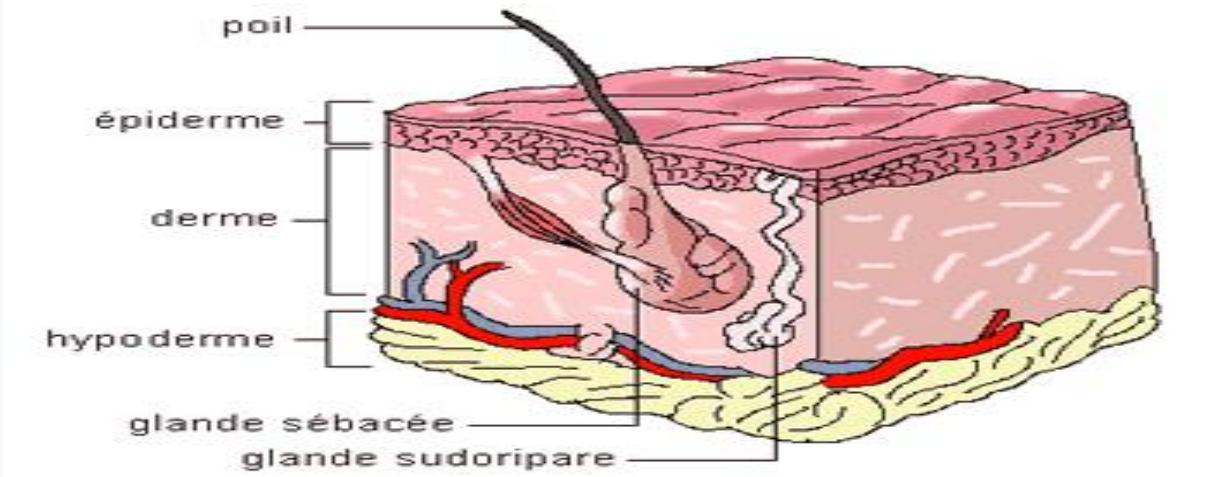
c. Gels These are liquids gelled using appropriate gelling agents. We distinguish between:

- Hydrophobic gels (oleogels): whose excipient can be liquid paraffin or fatty oil gelled by silicon dioxide, polyethylene, or colloidal aluminum or zinc soaps.

- Hydrophilic gels (hydrogels): composed essentially of water, glycerol, or PEGs gelled by tragacanth gum, starch, cellulose derivatives, or magnesium silicates.

d. Pastes These are semi-solid preparations containing a high proportion of powders finely dispersed in the excipient.

Reminder on skin structure:



Penetration through the skin. Penetration through the skin can occur: ♣ Through the keratinized layer ♣ Through the pilosebaceous unit. In summary: The skin constitutes a very effective barrier, but it can nevertheless be penetrated by small quantities of lipophilic substances capable of reaching the stratum corneum. If the substances also possess a certain degree of hydrophilicity, they can diffuse more deeply and sometimes even be absorbed systemically. Due to the reduced permeability of the skin, only a small fraction of the deposited substance is actually absorbed, and only highly active substances can have a systemic effect via this route (without passing through the liver).

- Factors influencing penetration through the skin:

• The nature of the active ingredient: The skin acts as a very selective living filter that only allows certain active ingredients to pass through, some through the epidermis, others through the pilosebaceous unit.
• Excipients forming the base of the ointment: Their chemical nature, physical and mechanical properties, lipophilicity or hydrophilicity, and the presence or absence of surfactants all play a role. They must be able to penetrate the pilosebaceous unit and readily release the active ingredient to the tissues they come into contact with. The partition coefficient should favor the tissues.

• Area of application: The stratum corneum is not uniform across the body. The skin is more keratinized on the palms and soles of the feet. Furthermore, penetration will be better in hairy areas.
• Skin hydration level: The degree of hydration can be influenced by the nature of the excipient. A hydrophobic excipient can form an occlusive coating that will keep the skin very moist. Conversely, a hygroscopic excipient can have the disadvantage of drying out the skin. One way to increase the

hydration of the stratum corneum is through occlusion, which, on the one hand, prevents its removal and, on the other hand, creates a hydration state conducive to facilitating the penetration of molecules, particularly moderately lipophilic molecules. • Blood flow: Certain areas are physiologically more vascularized, such as the face, neck, palms, and fingertips and toes.

• Application method: - Simple spreading or spreading combined with friction and massage: Massage increases local temperature and therefore vasodilation, which enhances penetration. - Application in layers of varying thicknesses. - Contact time of varying lengths and frequency of application.
• Skin condition
• Ointment pH

• Excipient selection criteria:

o It must have a suitable consistency to allow for easy spreading.

o It must be well-tolerated and have a low allergenic potential.

o It must have as few incompatibilities as possible with the other components of the ointment and the packaging.

o It must facilitate the penetration of the active ingredients into the tissues.

o It must be sufficiently stable to allow for good preservation.

o It should be washable with water, if possible, and not stain clothing.

o It should be sterilizable, if possible. Some examples of excipients used as an ointment base: ⁾ Glycerides • Lard • Vegetable oils • Hydrogenated oils ⁾ Waxes • Linolein • White wax • Spermaceti or spermaceti wax ⁾ Hydrocarbons • Petrolatum, paraffin, perhydrosqualene…

Preparation:

• Pharmacy: In the pharmacy, a mortar and pestle is used. Some ointments can be prepared at room temperature. This allows for a homogeneous mixture to be obtained by grinding together the active ingredients and excipients. Often, it is necessary to melt the excipients beforehand.

• Industry: The most commonly used equipment consists of planetary mixing units with a scraper and a set of various shaped whisks, chosen according to the consistency of the ointment: a simple hook for firmer ointments and whisks for others.

The mixer chamber must have a double jacket allowing the circulation of hot fluid during mixing and then cold fluid to ensure cooling.

• Propeller mixers or turbine agitators can be used.
• For emulsions: a die homogenizer or a colloidal mill.
• Method of introducing active ingredients: - Insoluble solid: finely powdered and sieved - Soluble solid: dissolved in the excipient - Emulsions: Lipid-soluble products in the oil phase; Water-soluble products in the aqueous phase
• Homogenization: Three-roll mill (smoother), Colloid mill.

Packaging: ν Jars ν Tubes - Bare aluminum or varnished interior. - Plastic.

Note: Ointments must be stored in tightly sealed containers; avoid cork stoppers as they harbor mold.
8. Control: ♣ Homogeneity ♣ Consistency determination - Viscosity - Hardness - Extrusion strength - Spreadability - Adhesion power ♣ pH ♣ Sterility ♣ Diffusion and bioavailability tests
Other forms intended for cutaneous application:

1. Powders for cutaneous application: These are preparations made up of dry, free-floating solid particles of varying fineness. They are available in single-dose or multi-dose form.

2. Liquid preparations for cutaneous application: These are solutions, emulsions, or suspensions that may contain one or more active ingredients in a suitable excipient. - Various solutions; including antiseptic preparations. - Shampoos; liquid or semi-liquid preparations intended for application to the scalp. - Liniments; intended for application to intact skin by rubbing and anointing. - Lotions; intended for application to the skin without rubbing. - Medicated foams; resulting from the dispersion of a large volume of gas in a liquid preparation containing one or more active ingredients and various adjuvants, including a surfactant that ensures its formation.
3. Cutaneous Adhesive Forms - Adhesive plasters; these are non-medicated items used to secure dressing material to the skin or simply to isolate or protect the skin. - Plasters; consisting of an

adhesive mass (or coating) containing one or more active ingredients, spread in a uniform layer on one of the substrates already described for adhesive plasters. - Medicated adhesive dressings; these consist of an adhesive plaster to which a dressing material (gauze) impregnated with an active ingredient, such as an antiseptic, is attached in its center. - Transdermal patches; these serve as a carrier or vehicle for one or more active ingredients intended to exert a systemic action after release and passage through the skin barrier. A transdermal system comprises: ν An outer substrate impermeable to the active ingredient. ν A reservoir containing the active ingredient in solid or semi-solid form. ν A removable protective film, removed at the time of application.

2. Suppository form:

PHARMACEUTICAL FORMS INTENDED FOR RECTAL ADMINISTRATION

Forms intended for this route are solid, semi-solid, or liquid; they are administered for local or systemic action. According to the pharmacopoeia, we distinguish: ▪ Rectal capsules. ▪ Rectal solutions and suspensions. ▪ Powders or tablets for rectal solutions or suspensions. ▪ Semi-solid rectal preparations. ▪ Rectal foams. ▪ Rectal tampons. ▪ Suppositories.

I. SUPPOSITORIES

This is a very old pharmaceutical form, used since antiquity: It was first used in local therapy (laxative, anti-hemorrhoidal, antiseptic), then for systemic purposes.

of a general action similar to medications administered orally or parenterally.

1. DEFINITION “Suppositories are solid, single-dose preparations. Their shape, volume, and consistency are adapted for rectal administration. They contain one or more active ingredients dispersed or dissolved in a suitable base which is, as appropriate, soluble or dispersible in water or melts at body temperature. They may also contain, if necessary, other excipients such as diluents, absorbents, surfactants, lubricants, antimicrobial preservatives, and colorants authorized by the competent authority.”

2. ADVANTAGES AND DISADVANTAGES OF THE SUPPOSITORY FORM

➢ Advantages - Allows the administration of medications that are irritating to the digestive tract or altered by gastric juices. - Facilitates use for infants. - Rapid absorption of the active ingredient because the rectum is highly vascularized. - Part of the active ingredients avoids the first-pass hepatic effect because the inferior and middle hemorrhoidal veins are connected to the iliac vein and not to the portal vein.

➢ Disadvantages - Many active ingredients are poorly absorbed in the rectum. - This form is not very popular. - Transport and administration are difficult during the day (requires refrigeration).

3. MODE OF ACTION ➢ Mechanical action - Laxative, e.g., glycerin-based suppositories ➢ Local action - Soothing or curative; anti-hemorrhoidal or anti-parasitic action. ➢ Systemic action - Direct venous route: the active ingredients pass rapidly into the inferior and middle hemorrhoidal veins that supply the rectal ampulla, then via the iliac veins, into the inferior vena cava and then into the heart, thus bypassing the liver and allowing for a systemic effect. - Indirect venous route: passage via the superior hemorrhoidal veins, the portal vein, and then through the liver. The general action obtained by rectal administration, although it does not appear to bypass the hepatic barrier 100%, nevertheless allows in various cases a faster action than that usually obtained by oral route.

4 ▪ Bioavailability The bioavailability of the suppository is determined by: ❑ Melting of the excipient: melting point, softening zone, viscosity (adjuvants) ❑ Dissolution rate: water-soluble excipient ❑ Diffusion in rectal fluids: solubility of the active ingredient in the excipient and in the fluids, and partition coefficient ❑ Absorption: location, pH of the medium, pKa of the active ingredient, its concentration, and its degree of division

5 MANUFACTURING SUPPOSITORIES BY MELT AND POUR

Given that the preparation of suppositories by melt and pour requires volumetric division of the mixture (active ingredient, excipient), the most critical aspect of the preparation is: what quantity of excipient should be introduced into a suppository formula to achieve accurate dosing? 5.1. Principle Densities

Identical active ingredient and excipients: In this case, the medication occupies the same volume for the same quantity of excipient. Example: Active ingredient…….0.10 g Excipient……q.s.p. a 2 g suppository The formula will be Active ingredient …….0.10 g Excipient…… 1.9 g

II. OTHER FORMS INTENDED FOR RECTAL ADMINISTRATION

1. Rectal Capsules ▪ Definition These are solid, single-dose preparations. They are soft, slightly elongated capsules, similar to suppositories. They are smooth and have a uniform external appearance. They contain an active ingredient dispersed in a paste or liquid excipient, often an oil to which an emulsifier is added to facilitate diffusion in the rectal ampulla.

2. Rectal Solutions, Emulsions, and Suspensions ▪ Liquid preparations intended for rectal administration (local, systemic, or diagnostic action)

3. Powders and tablets for rectal solutions or suspensions ▪ single-dose preparations dissolved or dispersed in water or other suitable solvents at the time of administration.

4. Semi-solid rectal preparations ▪ ointments, creams, or gels – packaged with a suitable device – meet the requirements of the monograph Semi-solid preparations for cutaneous application

5. Rectal foams ▪ Dispersion of a gas in a liquid containing a surfactant

6. Rectal tampons ▪ solid single-dose preparations intended for insertion into the lower rectum for a limited time.

7. Other rectal dosage forms (Under investigation) ▪ rectodispersible tablets ▪ self-emulsifying systems (SEDDS) ▪ microparticles ▪ nanoparticles and nanoformulations