CHAPTER 14

TOPICAL PREPARATIONS

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Abstract

Topical preparations are dosage forms designed for application to the skin or mucous membranes, offering localized drug delivery and systemic effects in some cases. This section covers various types of topical formulations, including creams, ointments, gels, and transdermal patches. The structure and barrier properties of the skin are discussed in relation to drug penetration and absorption. Formulation considerations for topical preparations, such as drug solubility, partition coefficient, and vehicle selection, are explored to optimize drug delivery. The role of penetration enhancers and their mechanisms of action are examined. Manufacturing processes for different topical dosage forms are outlined, including emulsification techniques for creams and fusion method for ointments. Rheological properties of semi-solid preparations and their impact on drug release and application are addressed. Quality control tests specific to topical preparations, including viscosity, spreadability, and in vitro release studies, are detailed. Special considerations for sterile ophthalmic preparations and their packaging requirements are discussed

Keywords: *Dermal delivery, Emulsions, Penetration enhancers, Rheology, Transdermal systems, Bioavailability*

Learning Objectives

After completion of the chapter, the student should be able to:

- Define topical preparations and their routes of administration.
- Classify different types of topical dosage forms and their applications.
- Explain the formulation principles of creams, ointments, gels, and patches.
- Describe the role of various excipients in topical preparations.
- Discuss the manufacturing processes for different topical dosage forms.
- Outline the quality control tests and stability considerations for topicals.
- Analyze the factors affecting drug absorption through the skin.

OINTMENTS

Ointments are soft semisolid preparations meant for external application to the skin or mucous membrane. They usually contain medicament, which is either dissolved or suspended in the base.

They have emollient and protective action.

Creams are semisolid emulsions for external application and are generally of softer consistency and lighter than ointments.

They are less greasy and are easy to apply.

Pastes are semisolid preparations for external application that differs from similar products in containing a high proportion of finely powdered medicaments. They are stiffer and are usually employed for their protective action

and for their ability to absorb serous discharges from skin lesions.

Thus when protective, rather than therapeutic action is desired, the formulation pharmacists will favor a paste, but when therapeutic action is required, he will prefer ointments and creams.

Jellies are transparent or translucent, non-greasy, semisolid preparation mainly used externally.

In these systems the liquid phase is entrapped within a three-dimensional polymeric matrix in which a high degree of physical cross-linking has been introduced.

The polymers (gelling agents) used include:

Natural Polymers : Tragacanth, pectin, carageenan, agar, alginic acid nd gelatin.

Synthetic and Semisynthetic polymers: Methyl cellulose, hydroxymethyl cellulose, carboxymethyl cellulose and Carbopols.

STRUCTURE OF SKIN

The skin has three main layers: the epidermis, dermis and hypodermis.

Epidermis is the outermost layer. It consists of:

(a) The *basal layer* (innermost) is one cell thick layer. Its cells divide constantly and the daughter cells are steadily pushed towards the surface.

(b) The *prickle cell layer*: The cells in this region are linked by tiny bridges or prickles.

(c) The *granular layer*: When they reach this region, the upwardly moving cells become granules and begin to synthesize the inert protein keratin.

(d) The *horny layer* (stratum corneum). This is the outermost layer and the cells are heavily keratinized and dead. The dead cells sloughs off gradually.

Dermis is the middle and the main part of the skin. The dermis is made up of protein collagen and elastin. The

collagen is in the form of gel that is reinforced by a framework of elastin.

Dermis contains the following structures:

(a) Blood vessels, lymphatics and nerves.
(b) Epidermal appendages e.g. hair follicles, sebaceous glands and sweat glands.

Hypodermis, the innermost layer, consists of adipose tissues. It gives physical protection and thermal insulation to underlying structures.

N.B.

Epidermis is non-granular but is penetrated by hair follicles, sebaceous glands and sweat glands.

Sebum is the secretion of sebaceous glands. Sebum is a mixture of fatty substances and emulsifiers; it mixes with water producing a fluid of pH 5.5 that covers the skin surface and permeates the upper layer of keratinized cells – this is called the "*acid-mantle*" of skin.

Keratin is hydrophillic, the stratum corneum normally contains about 20% w/w of water, the amount varying with atmospheric humidity. This moisture keeps the skin supple and if its level falls below about 12% the cells becomes dry and brittle and then shrink and curl at the edges, making the skin feel rough.

Cracking may follow, causing discomfort. Loss of water may be the result of excessive evaporation, over-usage of detergents (which removes sebum) and cold weather (which inhibits sebum production).

PERMEABILITY OF DRUG THROUGH EPIDERMIS

Most dermatological preparations belong to one of tw classes:

1. *Preparation intended to remain on the surface*

e.g. products for penetration or for emollient action.

2. *Preparations intended to penetrate the skin but will not enter into blood stream*

Drugs penetrate the epidermis by two man routes:
(a) Through the keratinized cells of the stratum corneum.
The keratinized cells are fused together so drug molecules directly diffuse through them. These cells contains keratin which is hydrophilic and phospholipids which is hydrophobic, so drug molecules having solubility in both water and oil have good permeability through this route.
(b) Via hair follicles
Although the hair follicles occupy only a small area of the total epidermis, they provide a very important route of penetration. The fat soluble drugs dissolve in sebum, diffuses in to the sebum-filled follicles and passes to dermis.

FACTOR AFFECTING PERMEABILITY OF A DRUG THROUGH SKIN

A. **Factor associated with the skin**
(a) *Hydration of the horny layer*
The hydration of keratinized cells is raised by covering the area with a moisture-proof plastic film to prevent evaporation of perspiration. Hydration increases the drug penetration.
(b) *Thickness of the horny layer*
The horny layer is thickest on palms and soles and thinnest on the face; penetration rate increases with decreased thickness of horny layer.
(c) *Skin condition*
The permeability of the skin is affected by age, disease, climate and injury. For xample, absorption occurs rapidly in children and if the dermis is exposed by a wound or burn.

B. **Factors associated with the medicament**
(a) *Solubility of the drug*
Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

(b) *Dissociation constant (pKa)*

If a drug is ionized in the surrounding pH of the dermis then the penetration of the ionic species are restricted by electrostatic interactions. Degree of ionization depends on the pKa of the drug.

e.g. Methyl salicylate and methyl nicotinate penetrate much faster than salicylic acid and nicotinic acid respectively.

(c) *Particle size*

Reducing the particle size increases the dissolution of a poorly soluble drug in suspension and thus increases the release rate from the vehicle.

(d) *Crystal structure*

The metastable polymorph is much more soluble than its stable form, so the release of drug in metastable state is much more faster than stable form.

C. **Factors associated with vehicles**

The rate of release of a drug from a vehicle to stratum corneum is governed by *vehicle-to-stratum corneum partition coefficient*. The thermodynamic activity of the drug in the vehicle is the product of the concentration of the drug and the activity coefficient (γ) of the drug in the vehicle. Drugs held firmly by the vehicle exhibit low activity coefficient, hence slow rate of release from that drug-vehicle combination. Drug held loosely by the vehicle shows higher activity coefficient, hence shows faster rate of release.

The vehicles may enhance the penetration of a drug in one or more of the following ways:-

a) By ensuring good contact with the surface of the body
b) By increasing the degree of hydration of the stratum corneum
c) By penetrating the epidermis
d) By directly altering the permeability of the skin

(a) <u>Contact with body surface</u>

Sticky bases such as soft paraffin, Paraffin ointment B.P.C.,

Simple ointment B.P. etc. adheres well to the skin but are difficult to apply evenly and remove completely.
Creams are easier to apply and remove. Oil in water (o/w) creams mix with sebum and are more suitable for weeping or wounded surface.
(b) Hydration of stratum corneum
An occlusive layer reduces evaporation of water from skin, increasing hydration of the horny layer and, therefore, promotes penetration of medicament.
e.g. hydrocarbons, wool fat and isopropyl myristate containing ointments produce occlusive films on the skin. Water in oil (o/w) type creams have some occlusive effects.
Humectants like glycerols are not good for retaining water because at low atmospheric humidities, because they tend to increase loss of water by absorbing it from the skin.
(c) Penetration of the epidermis
Bases miscible with the sebum penetrate into the regions of the skin in which sebum is found.
e.g. Woolfat (originating from sebaceous glands of sheep) penetrates into the skin.
Vegetable oils penetrate more slowly and liquid paraffin does not penetrate at all.
(d) Alteration of skin permeability
Penetration can be improved by dissolving the medicament in an organic liquid such as ethanol, dimethylformamide(DMF), dimethyl acetamide, dimethylsulfoxide (DMSO) and propylene glycol. They increases the hydration of skin.

Characteristics of an ideal ointment:

1. It should be chemically and physically stable.
2. It should be smooth and free from grittiness.
3. It should melt or soften at body temperature and be easily applied.
4. The base should be non-irritant and should have no

therapeutic action.

5. The medicament should be finely divided and uniformly distributed throughout the base.

Classification of ointments

According to their therapeutic properties based on penetration of skin.

(a) Epidermic, (b) Endodermic, (c) Diadermic

(a) Epidermic ointments

These ointments are intended to produce their action on the surface of the skin and produce local effect.

They are not absorbed.

They acts as protectives, antiseptics and parasiticides.

(b) Endodermic ointments

These ointments are intended to release the medicaments that penetrate into the skin. They are partially absorbed and acts as emollients, stimulants and local irritants.

(c) Diadermic ointments

These ointments are intended to release the medicaments that pass through the skin and produce systemic effects.

OINTMENT BASES

The ointment base is that substance or part of an ointment preparation which serves as carrier or vehicle for the medicament.

An ideal ointment base should be inert, stable, smooth, compatible with the skin, non-irritating and should release the incorporated medicaments readily.

Classification of ointment bases:

1. Oleaginous bases
2. Absorption bases
3. Water-miscible bases
4. Water soluble bases