

CHAPTER 6.**SEMISOLID DOSAGE FORMS***Syllabus*

Ointment bases: oleaginous bases, hydrocarbon and silicon containing bases.

Absorption bases, emulsion bases, water soluble bases.

Preparation and preservation of these ointments with industrial equipment used for processing.

Questions:

1. Define and differentiate between Ointment and creams, lotion and liniment. (98) [4+4]
2. Give different ointment bases with examples. (98)[8]
3. Discuss various methods for manufacturing of ointments. [8]
4. Write a note on different types of raw materials that are used in the manufacture of semisolid dosage forms. What are the factors that affect skin penetration of drugs from semisolids (96)[16]
5. Preservative in ointment. (95) [4]
6. How do you select the ointment base for a water soluble and insoluble drug to be incorporated for a medicinal preparation. Discuss on the selection of ointment base (94) [16]
7. Discuss on the importance of packing materials for ointments. What is the influence of packing materials for ointment storage? (94) [16]
8. Write in brief the factors governing the selection of ointment bases. (93) [6]
9. Give the characteristics and examples of oleaginous bases. (93)[6]
10. Discuss the different methods of ointment preparations. (93) [4]

INTRODUCTION

Pharmaceutical semisolid dosage preparations include ointments, pastes, cream, emulsions, gels and rigid foams.

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 and 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 slough 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 hydrophilic, 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 become 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 two 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 main 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 contain 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, diffuse in to the sebum-filled follicles and pass 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 example, 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 enter through hair follicles. Moderately lipid soluble molecules penetrate 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 is 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) Contact with body surface

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 increase the hydration of skin.

OINTMENT

Definition: Ointments are semisolid preparations for application to the skin or mucosae. The ointment bases are almost always anhydrous and generally contains one or more medicaments in suspension or solution.

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 act 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 act 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

OLEAGINOUS BASES

These bases consists of oils and fats. The most important are the

Hydrocarbons i.e. petrolatum, paraffins and mineral oils.

The *animal fat* includes lard.

The combination of these materials can produce a product of desired melting point and viscosity.

(a) Petrolatum (Soft paraffin)

This is a purified mixture of semi-solid hydrocarbons obtained from petroleum or heavy lubricating oil.

Yellow soft paraffin (Petrolatum; Petroleum jelly)

This a purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain suitable stabilizers like, antioxidants e.g. α -tocopherol (Vitamin E), butylated hydroxy toluene (BHT) etc.

Melting range : 38 to 56°C.

White soft paraffin (White petroleum jelly, White petrolatum)

This a purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or partially decolorized by percolating the yellow soft paraffin through freshly burned bone black or adsorptive clays.

Melting range : 38 to 56°C.

Use: The white form is used when the medicament is colourless, white or a pastel shade. This base is used in

Dithranol ointment B.P.

Ammoniated Mercury and Coal tar ointment B.P.C.

Zinc ointment B.P.C.

(b) Hard paraffin (Paraffin)

This is a mixture of solid hydrocarbons obtained from petroleum.

It is colourless or white, odorless, translucent, wax-like substance. It solidifies between 50 and 57°C and is used to stiffen ointment bases.

(c) Liquid paraffin (Liquid petrolatum,; White mineral oil)

It is a mixture of liquid , hydrocarbons obtained from petroleum. It is transparent, colourless, odourless, viscous liquid.

On long storage it may oxidize to produce peroxides and therefore, it may contain tocopherol or BHT as antioxidants.

It is used along with hard paraffin and soft paraffin to get a desired consistency of the ointment. Tubes for eye, rectal and nasal ointments have nozzles with narrow orifices through which it is difficult to expel very viscous ointments without the risk of bursting the tube. To facilitate the extrusion upto 25% of the base may be replaced by liquid paraffins.

Advantages of hydrocarbons bases:

- (i) They are not absorbed by the skin. They remain on the surface as an occlusive layer that restricts the loss of moisture hence, keeps the skin soft.
- (ii) They are sticky hence ensures prolonged contact between skin and medicament.
- (iii) They are almost inert. They consist largely of saturated hydrocarbons, therefore, very few incompatibilities and little tendency of rancidity are there.
- (iv) They can withstand heat sterilization, hence, sterile ophthalmic ointments can be prepared with it.
- (v) They are readily available and cheap.

Disadvantages of hydrocarbon bases;

- (i) It may lead to water logging followed by maceration of the skin if applied for a prolonged period.
- (ii) It retains body heat, which may produce an uncomfortable feeling of warmth.
- (iii) They are immiscible with water; as a result rubbing onto the surface and removal after treatment both are difficult.
- (iv) they are sticky, hence makes application unpleasant and leads to contamination of clothes.
- (v) Water absorption capacity is very low, hence, these bases are poor in absorbing exudate from moist lesions.

ABSORPTION BASE

The term absorption base is used to denote the water absorbing or emulsifying property of these bases and not to describe their action on the skin.

These bases (some times called *emulsifiable ointment bases*) are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantity of water yet retaining its ointment-like consistency.

Preparations of this type do not contain water as a component of their basic formula but if water is incorporated a W/O emulsion results.

Wool Fat (anhydrous lanolin)

It is the purified anhydrous fat like substance obtained from the wool of sheep.

- It is practically insoluble in water but can absorb water upto 50% of its own weight. Therefore it is used in ointments the proportion of water or aqueous liquids to be incorporated in hydrocarbon base is too large.
- Due to its sticky nature it is not used alone but is used along with other bases in the preparation of a number of ointments.

e.g. Simple ointment B.P. contains 5% and the B.P. eye ointment base contains 10% woolfat.

Hydrous Wool Fat (Lanolin)

- It is a mixture of 70 % w/w wool fat and 30 % w/w purified water. It is a w/o emulsion. Aqueous liquids can be emulsified with it.
- It is used alone as an emollient.
- Example:- Hydrous Wool Fat Ointment B.P.C., Calamine Coal Tar Ointment.

Wool Alcohol

It is the emulsifying fraction of wool fat. Wool alcohol is obtained from wool fat by treating it with alkali and separating the fraction containing cholesterol and other alcohols. It contains not less than 30% of cholesterol.

Use:-

- It is used as an emulsifying agent for the preparation of w/o emulsions and is used to absorb water in ointment bases.
- It is also used to improve the texture, stability and emollient properties of o/w emulsions.

Examples :- Wool alcohol ointment B.P. contains 6% wool alcohol and hard, liquid and soft paraffin.

Beeswax

It is purified wax, obtained from honey comb of bees.

It contains small amount of cholesterol. It is of two types: (a) yellow beeswax and (b) white beeswax.

Use:-

Beeswax is used as a stiffening agent in ointment preparations.

Examples:-Paraffin ointment B.P.C. contains beeswax.

Cholesterol

It is widely distributed in animal organisms. Wool fat is also used as a source of cholesterol.

Use:- It is used to increase the water absorbing power of an ointment base.

Example:- Hydrophilic petroleum U.S.P. contains:

| | |
|---------------------|-----|
| Cholesterol | 3% |
| Stearyl alcohol | 3% |
| White beeswax | 8% |
| White soft paraffin | 86% |

Advantages of absorption bases:

- They are less occlusive nevertheless, are good emollient.
- They assist oil soluble medicaments to penetrate the skin.
- They are easier to spread.
- They are compatible with majority of the medicaments.
- They are relatively heat stable.
- The base may be used in their anhydrous form or in emulsified form.
- They can absorb a large quantity of water or aqueous substances.

Disadvantages: Inspite of their hydrophilic nature, absorption bases are difficult to wash.

WATER MISCIBLE BASES

They are miscible with an excess of water. Ointments made from water-miscible bases are easily removed after use.

There are three official anhydrous water-miscible ointment bases:-

Example:-

Emulsifying ointment B.P. – contains anionic emulsifier.

Cetrimide emulsifying ointment B.P. – contains cationic emulsifier

Cetomacrogol emulsifying ointment B.P. – contains non-ionic emulsifier

Uses: they are used to prepare o/w creams and are easily removable ointment bases

e.g. Compound Benzoic Acid Ointment (Whitfield's Ointment) – used as antifungal ointment.

Advantages of water miscible bases:

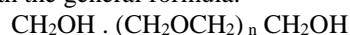
- Readily miscible with the exudates from lesions.
- Reduced interference with normal skin function.
- Good contact with the skin, because of their surfactant content.
- High cosmetic acceptability, hence there is less likelihood of the patients discontinuing treatment.
- Easy removal from the hair.

WATER SOLUBLE BASES

Water soluble bases contain only the water soluble ingredients and not the fats or other greasy substances, hence, they are known as grease-less bases.

Water soluble bases consists of water soluble ingredients such as polyethylene glycol polymers (PEG) which are popularly known as “carbowaxes” and commercially known as “macrogols”.

They are a range of compounds with the general formula:



The PEGs are mixtures of polycondensation products of ethylene and water and they are described by numbers representing their average molecular weights. Like the paraffin hydrocarbons they vary in consistency from viscous liquids to waxy solids.

Example:-

| | |
|----------------------------------|----------------------|
| Macrogols 200, 300, 400 | – viscous liquids |
| Macrogols 1500 | – greasy semi-solids |
| Macrogols 1540, 3000, 4000, 6000 | – waxy solids. |

Different PEGs are mixed to get an ointment of desired consistency.

Advantages of PEGs as ointment base:

- They are water soluble; hence, very easily can be removed from the skin and readily miscible with tissue exudates.
- Helps in good absorption by the skin.
- Good solvent properties. Some water-soluble dermatological drugs, such as salicylic acid, sulfonamides, sulfur etc. are soluble in this bases.
- Non-greasy.
- They do not hydrolyze, rancidify or support microbial growth.
- Compatibility with many dermatological medicaments.

Disadvantages:

- Limited uptake of water. Macrogols dissolve when the proportion of water reaches about 5%.
- Reduction in activity of certain antibacterial agents, e.g. phenols, hydroxybenzoates and quaternary compounds.
- Solvent action on polyethylene and bakelite containers and closures.

Certain other substances which are used as water soluble ointment bases include tragacanth, gelatin, pectin, silica gel, sodium alginate, cellulose derivatives, etc.

FACTORS GOVERNING SELECTION OF AN IDEAL OINTMENT BASE

- Dermatological factors
- Pharmaceutical factors

1. Dermatological factors

(a) Absorption and Penetration:

‘Penetration’ means passage of the drug across the skin i.e. cutaneous penetration, and ‘absorption’ means passage of the drug into blood stream.

- Medicaments which are both soluble in oil and water are most readily absorbed through the skin.
- Whereas animal and vegetable fats and oils normally penetrate the skin.
- Animals fats, e.g. lard and wool fat when combined with water, penetrates the skin.
- o/w emulsion bases release the medicament more readily than greasy bases or w/o emulsion bases.

(b) Effect on the skin

- Greasy bases interfere with normal skin functions i.e. heat radiation and sweating. They are irritant to the skin.
- o/w emulsion bases and other water miscible bases produce a cooling effect due to the evaporation of water.

(c) Miscibility with skin secretion and sebum

Skin secretions are more readily miscible with emulsion bases than with greasy bases. Due to this the drug is more rapidly and completely released to the skin.

(d) Compatibility with skin secretions:

The bases used should be compatible with skin secretions and should have pH about 5.5 because the average skin pH is around 5.5. Generally neutral ointment bases are preferred.

(e) Non-irritant

All bases should be highly pure and bases specially for eye ointments should be non-irritant and free from foreign particle.

(f) Emollient properties

Dryness and brittleness of the skin causes discomfort to the skin therefore, the bases should keep the skin moist. For this purpose water and humectants such as glycerin, propylene glycol are used. Ointments should prevent rapid loss of moisture from the skin.

(g) Ease of application and removal

The ointment bases should be easily applicable as well as easily removable from the skin by simple washing with water. Stiff and sticky ointment bases require much force to spread on the skin and during rubbing newly formed tissues on the skin may be damaged.

2. Pharmaceutical factors

(a) Stability

Fats and oils obtained from animal and plant sources are prone to oxidation unless they are suitably preserved. Due to oxidation odour comes out. This type of reactions are called *rancidification*. Lard, from animal origin, rancidify rapidly. Soft paraffin, simple ointment and paraffin ointment are inert and stable. Liquid paraffin is also stable but after

prolonged storage it gets oxidized. Therefore, an antioxidant like *tocopherol* (Vit -E) may be incorporated. Other antioxidants those may be used are *butylated hydroxy toluene* (BHT) or *butylated hydroxy anisole* (BHA).

(b) Solvent properties

Most of the medicaments used in the preparation of ointments are insoluble in the ointment bases therefore, they are finely powdered and are distributed uniformly throughout the base.

(c) Emulsifying properties

Hydrocarbon bases absorbs very small amount of water.

Wool fat can take about 50% of water and when mixed with other fats can take up several times its own weight of aqueous solution.

Emulsifying ointment, cetrimide emulsifying ointment and cetomacrogol emulsifying ointment are capable of absorbing considerable amount of water, forming w/o creams.

(d) Consistency

The ointments produced should be of suitable consistency. They should neither be hard nor too soft. They should withstand climatic conditions. Thus in summer they should not become too soft and in winter not too hard to be difficult to remove from the container and spread on the skin.

The consistency of an ointment base can be controlled by varying the ratio of hard and liquid paraffin.

PREPARATION OF OINTMENTS

A well-made ointment is –

(a) *Uniform throughout* i.e. it contains no lumps of separated high melting point ingredients of the base, there is no tendency for liquid constituents to separate and insoluble powders are evenly dispersed.

(b) *Free from grittiness*, i.e. insoluble powders are finely subdivided and large lumps of particles are absent. Methods of preparation must satisfy this criteria.

Two mixing techniques are frequently used in making ointments:

1. **Fusion**, in which ingredients are melted together and stirred to ensure homogeneity.
2. **Trituration**, in which finely-subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.

1. **Ointments prepared by Fusion method:**

When an ointment base contain a number of solid ingredients such as white beeswax, cetyl alcohol, stearyl alcohol, stearic acid, hard paraffin, etc. as components of the base, it is required to melted them. The melting can be done in two methods:

Method-I

The components are melted in the decreasing order of their melting point i.e. the higher m.p. substance should be melted first, the substances with next melting point and so on. The medicament is added slowly in the melted ingredients and stirred thoroughly until the mass cools down and homogeneous product is formed.

Advantages:

This will avoid over-heating of substances having low melting point.

Method-II

All the components are taken in subdivided state and melted together.

Advantages:

The maximum temperature reached is lower than Method-I, and less time was taken possibly due to the solvent action of the lower melting point substances on the rest of the ingredients.

Cautions:

- (i) Melting time is shortened by grating waxy components (i.e. beeswax, wool alcohols, hard-paraffin, higher fatty alcohols and emulsifying waxes) by stirring during melting and by lowering the dish as far as possible into the water bath so that the maximum surface area is heated.
- (ii) The surface of some ingredients discolors due to oxidation e.g. wool fats and wool alcohols and this discolored layers should be removed before use.
- (iii) After melting, the ingredients should be stirred until the ointment is cool, taking care not to cause localized cooling, e.g. by using a cold spatula or stirrer, placing the dish on a cold surface (e.g. a plastic bench top) or transferring to a cold container before the ointment has fully set. If these precautions are ignored, hard lumps may separate.
- (iv) Vigorous-stirring, after the ointment has begun to thicken, causes excessive aeration and should be avoided.
- (v) Because of their greasy nature, many constituents of ointment bases pickup dirt during storage, which can be seen after melting. This is removed from the melt by allowing it to sediment and decanting the supernatant, or by passage through muslin supported by a warm strainer. In both instances the clarified liquid is collected in another hot basin.
- (vi) If the product is granular after cooling, due to separation of high m.p. constituents, it should be remelted, using the minimum of heat, and again stirred and cooled.

Example:

(i) **Simple ointment B.P. contains**

| | |
|---------------------|------|
| Wool fat | 50g |
| Hard paraffin | 50g |
| Cetostearyl alcohol | 50g |
| White soft paraffin | 850g |

Type of preparation: Absorption ointment base

Procedure:

Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted. If required decanted or strained and stirred until cold and packed in suitable container.

(ii) **Paraffin ointment base**

Type of preparation: Hydrocarbon ointment base

(iii) **Wool alcohols ointment B.P.**

Type of preparation: Absorption base

(iv) **Emulsifying ointment B.P.**

Type of preparation: Water-miscible ointment base.

(v) **Macrogol ointment B.P.C**

Type of preparation: Water soluble ointment base

Formula: Macrogol 4000
Liquid Macrogol 300

Method: Macrogol 4000 is melted and previously warmed liquid macrogol 300 is added. Stirred until cool.

2. OINTMENT PREPARED BY TRITURATION

This method is applicable in the base or a liquid present in small amount.

- (i) Solids are finely powdered are passed through a sieve (# 250, # 180, #125).
- (ii) The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.
- (iii) Finally liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment an thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Example:

(i) Whitfield ointment (Compound benzoic acid ointment B.P.C.)

Formula: Benzoic acid, in fine powder 6gm
Salicylic acid, in fine powder 3gm
Emulsifying ointment 91gm

Method: Benzoic acid and salicylic acid are sieved through No. 180 sieves. They are mixed on the tile with small amount of base and levigated until smooth and dilute gradually.

(ii) Salicylic acid sulphur ointment B.P.C.

3. OINTMENT PREPARATION BY CHEMICAL REACTION

Chemical reactions were involved in the preparation of several famous ointments of the past, e.g. Strong Mercuric Nitrate Ointment, of the 1959 B.P.C.

(a) **Ointment containing free iodine**

Iodine is only slightly soluble in most fats and oils but readily soluble.

Iodine is readily soluble in concentrated solution of potassium iodide due to the formation of molecular complexes $KI.I_2$, $KI.2I_2$, $KI.3I_2$ etc.

These solutions may be incorporated in absorption-type ointment bases.

e.g. *Strong Iodine Ointment B.Vet.C* (British Veterinary Pharmacopoeia) is used to treat ringworm in cattle. It contains free iodine. At one time this type of ointments were used as counter-irritants in the treatment of human rheumatic diseases but they were not popular because:

They stain the skin a deep red color.

- (i) Due to improper storage the water dries up and the iodine crystals irritate the skin, hence glycerol was some times added to dissolve the iodine-potassium iodide complex instead of water.

Example: Strong Iodine Ointment B. Vet.C.

Iodine
Woolfat
Yellow soft paraffin
Potassium iodide
Water

MANUFACTURE OF OINTMENTS / CREAMS IN INDUSTRIAL SCALE

1. Preparation of oil and aqueous phase

Oils + Fats

↓ *Equipment: Steam jacketed kettle*

Melted and mixed

↓

Strained through several layers of cheese cloths to remove foreign matter

Water soluble ingredients + Purified water

↓ *Equipment: Mechanical stirrer*

Dissolved

↓

Filtered

↓

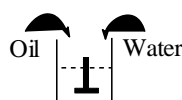
Heated to the melting point of oil phase

- Cakes, flakes or powdered waxes are directly weighed in a physical balance.
- Semisolid petrolatum is melted in the container supplied by an immersion heater, the liquid petrolatum is then transferred by a *metering pump* through *metal reinforced inert plastic hoses and insulated pipes*.

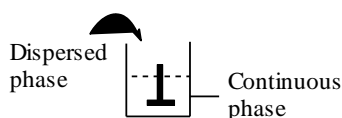
2. Mixing of oil and water phases

Mixing temperature is 70–72°C for proper mixing.

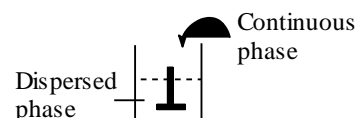
Three methods of mixing are there:

(A) Simultaneous blending

- For continuous or large batch operation
- *Equipments*
Proportioning pump
Continuous mixer

(B) Addition of disperse phase to continuous phase

- For an emulsion having low volume of dispersed phase.
- *Equipment:*
Simple metering pump

(C) Addition of continuous phase to disperse phase

- For an emulsion formed by phase inversion method.
- *Equipment:*
Simple metering pump.

- Batch sizes are on weight basis. For weighing a *hydraulic load cell* is fitted under one of the leg of the mixing kettle.

3. Cooling the semisolid

Cooling should be slow to prevent crystallization of high m.p. waxes. Perfumes are added at 43 to 45°C.

Equipments: Kettle fitted with heating / cooling arrangements, agitator and sweep blades (for scrapping the wall).

Cooled to 43 to 45°C

↓

Kettle with agitator and sweep blades

Addition of perfume

↓

Addition of drug powder

↓

Dispersed or dissolved

4. Homogenization

Creams or ointments

↓

Equipment: Low-shear gear pump and roller mill / colloid mill / valve type homogenizer

Homogenization

5. Storage of semisolids

Stored before packaging. In the mean time Q.C. report comes. Stored in a tight-fitting stainless steel (SS#316) container.

6. Transfer of materials for packaging*Equipment:* Ointment filling machine

Washing of the equipments with high-pressure (up to 1000psi), low-volume pumps and hot water and detergents should be done.

To sterilize the equipments, containers, pumps and other accessories are flushed with chlorinated water or formalin – followed by rinsing them with bacteria free water.

STABILITY OF OINTMENTS

The ointments should remain stable from the time of preparation to the time when the whole of it is consumed by the user.

- (i) To stop microbial growth preservatives are added. Preservatives for ointment includes : p-hydroxy benzoates, phenol, benzoic acid, sorbic acid, methyl paraben, propyl paraben, quaternary ammonium compounds, mercury compounds etc.
- (ii) The preservatives should not react with any of the component of the formulation. Plastic containers may absorb the preservative and thereby decreasing the concentration of preservative available for killing the bacteria.
- (iii) Some ingredients like wool fat and wool alcohols are susceptible to oxidation. Therefore, a suitable antioxidant may be incorporated to protect the active ingredients from oxidation.
- (iv) Incompatible drugs, emulsifying agents and preservatives must be avoided. The drugs which are likely to hydrolyze must be dispensed in an anhydrous base.
- (v) Humectants such as, glycerin, propylene glycol and sorbitol may be added to prevent the loss of moisture from the preparation.
- (vi) Ointment must be stored at an optimum temperature otherwise separation of phases may take place in the emulsified products which may be very difficult to remix to get a uniform product.

Preservatives in ointments