**SEMISOLID DOSAGE FORMS**

**Definition:** Semi solid pharmaceutical system comprise a body of product ,which when applied to skin or accessible mucous membranes tends to alleviate or treat a pathological condition or other protection against harmful environment.

**Ideal properties of Semi solid dosage form:**

1. **Physical properties**
* Smooth texture
* Elegant in appearance
* Non dehydrating
* Non gritty
* Non greasy and non staining
* Non hygroscopic
1. **Physiological properties**
* Non irritating
* Do not alter membrane function
* Miscible with skin secretion
1. **Application properties**
* Easy applicable with efficient drug release
* High aqueous washibility

**TYPES OF SEMI-SOLID DOSAGE FORMS**

1. OINTMENTS

Ointments are homogenous, translucent, viscous, semi solid preparation intended for external application to skin or mucous membranes. Ointment may be medicated or not.

* Uses
	+ Emollient
	+ Application for active ingredients to the skin
	+ Occulsive

2. CREAMS

* Viscous semisolid emulsion with opaque appearance as contrasted with translucent ointments
* Consistency depends on whether the cream is W/O or O/W

3. PASTES

* Contains high percentage of insoluble solid (usually 50% or more)
* Pastes are usually prepared by incorporating solids directly into a congealed system by levigation with a portion of base to form paste like mass.
* They have good adhesion on skin and less greasy.

4. POULTICES

* They are solid masses of solid matter applied to skin in order to reduce inflammation and in some cases to act as a counter irritant.
* Poultices must retain heat for a considerable time.
* After heating the preparation is spread on dressing and applied to the affected area.

5. GELS & JELLIES

* Gels are semi solid system in which liquid phase is constrained with a 3-D polymeric matrix having a high degree of physical or chemical cross linking
* Gels are aqueous colloidal system of hydrated forms of insoluble medicaments.
* Jellies are transparent or translucent non greasy semisolid and contain more water than gels.
* Used for medication and lubrication

**Types of gel-PHASE**

* **Single Phase**
	+ **Gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid**
	+ **Usually involve organics**
* **Two Phase(Domain)**
	+ **When the gel mass consists of floccules of small distinct particles**
	+ **Usually involve inorganics**



**Gel Composition**

* Gelling agent
* Water
* Cosolvents
* Preservatives
* Stabilizers

**Kinds of Gels**

* Hydrogels
	+ Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
* Organic Gels
	+ Contain an organic liquid (e.g., Plastibase)
* Carbomer Gels
	+ Aqueous dispersion neutralized with sodium hydroxide or triethanolamine
* Methylcellulose Gels
* Starch Glycerite
* Aluminum Hydroxide Gel

**Gelling agents**

* Gelling agent forms a gel dissolves in a liquid phase as a colloid mixture that forms a weakly cohesive internal structure.
* These are organic hydrocolloids or hydrophillic inorganic substances.

Example: tragacanth, sodium alginate, pectin, gelatin, cellulose derivatives.

|  |  |
| --- | --- |
| **Material**  | **%**  |
| Carbomer 94 1 resin NF  | 0.15  |
| Carbomer 94 1 resin NF | 0.25  |
| Guar gum  | 1.50  |
| Methyl cellulose  | 2.00  |
| Sodium alginate  | 2.50  |

FACTOR AFFECTING PERMEABILITY OF A DRUG THROUGH SKIN

A. **Factor associated with the skin**

1. 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.

1. 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.

1. 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**

1. Solubility of the drug

Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

1. 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.

1. 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.

1. 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:-

1. By ensuring good contact with the surface of the body
2. By increasing the degree of hydration of the stratum corneum
3. By penetrating the epidermis
4. 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 increases the hydration of skin.

**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.

**INGREDIENTS FOR SEMI SOLID DOSAGE FORMS:**

* Active pharmaceutical ingredients
* Bases
* Preservatives
* Humectants
* Anti oxidants
* Emulsifier
* Gelling agent
* Permeation enhancer
* Buffers

**Bases**:

* It is one of the most important ingredient used in the formulation of semisolid dosage form
* Ointments and suppository base do not merely acts as the carrier of the medicaments, but they also control the extent of absorption of medicaments incorporated with them

Base should be:

* Compatible with skin ph and drug
* Inert ,non irritating and non sensitizing
* Good solvent and/or emulsifying agent
* Emollient , protective , non greasy and easily removable
* Release medicaments easily at the site of administration
* Pharmaceutical elegant and possess good stability.

**Types of bases:**

1. Oleaginous bases
2. Absorption bases
3. Water miscible or emulsion bases
4. Water soluble bases
5. **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.
1. **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 560C.

**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 560C.
* 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 570C 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:**

1. 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.
2. They are sticky hence ensures prolonged contact between skin and medicament.
3. They are almost inert. They consist largely of saturated hydrocarbons, therefore, very few incompatibilities and little tendency of rancidity are there.
4. They can withstand heat sterilization, hence, sterile ophthalmic ointments can be prepared with it.
5. They are readily available and cheap.

**Disadvantages of hydrocarbon bases;**

1. It may lead to water logging followed by maceration of the skin if applied for a prolonged period.
2. It retains body heat, which may produce an uncomfortable feeling of warmth.
3. They are immiscible with water; as a result rubbing onto the surface and removal after treatment both are difficult.
4. They are sticky, hence makes application unpleasant and leads to contamination of clothes.
5. 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 (sometimes 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.
1. 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)**

1. 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.
2. It is used alone as an emollient.
3. 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:

1. It is used as an emulsifying agent for the preparation of w/o emulsions and is used to absorb water in ointment bases.
2. 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:**

1. They are less occlusive nevertheless, are good emollient.
2. They assist oil soluble medicaments to penetrate the skin.
3. They are easier to spread.
4. They are compatible with majority of the medicaments.
5. They are relatively heat stable.
6. The base may be used in their anhydrous form or in emulsified form.
7. 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:**

1. Readily miscible with the exudates from lesions.
2. Reduced interference with normal skin function.
3. Good contact with the skin, because of their surfactant content.
4. High cosmetic acceptability, hence there is less likelihood of the patients discontinuing treatment.
5. 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:

 CH2OH . (CH2OCH2) n CH2OH

* 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:**

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

**Disadvantages:**

1. Limited uptake of water. Macrogols dissolve when the proportion of water reaches about 5%.
2. Reduction in activity of certain antibacterial agents, e.g. phenols, hydroxybenzoates and quaternary compounds.
3. 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**

1. Dermatological factors

2. 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.

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

(b) Effect on the skin

1. Greasy bases interfere with normal skin functions i.e. heat radiation and sweating. They are irritant to the skin.
2. 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.

**Preservatives**:

Some bases, although, resist microbial attack but because of their high water content, it require an anti microbial preservative.

* Commonly used preservative include: **Methyl hydroxy benzoate, Propyl hydroxy benzoate**, **Chorocresol, Benzoic acid, Phenyl mercuric nitrate**

**Antioxidants:**

* Oxygen is highly reactive atom that is capable of becoming of potentially damaging molecules commonly called “free radicals”.
* Free radicals are capable of attacking the healthy cells of the body, causing them to loose their structure and functions
* To prevent this an anti oxidant is added.
* Example : **Butylated hydroxy anisole , Butylated hydroxy toluene**

|  |  |  |
| --- | --- | --- |
| **ANTIOXIGENS**  | **REDUCING AGENT**  | **ANTIOXIDANT** **SYNERGIST**  |
| Acts by reacting with the free radicals.e.g.* Butylated hydroxy anisole (BHA)
* Butylated hydroxy tocopherols (BHT)

(used for oil system)  | Have lower redox potential than drug,hence gets oxidized first.e.g.* Ascorbic acid
* Potassium and sodium metabisulfite
* Thiosulfite

(used for aqueous system) | Chelating or sequestering agents, enhance the effect of anti oxidants.e.g.* Citric acid
* Tartaric acid
* Lacithin
 |

**Humectants**:

A humectant is a hygroscopic substance . It is often a molecule with several hydrophilic groups, most often hydroxl group.

Humectants are used to:

* **Increase the solubility of active ingredients**
* **To elevate its skin preparation**
* **Elevate the hydration of the skin.**

**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:

1. 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.
2. 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.
3. 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.
4. Vigorous-stirring, after the ointment has begun to thicken, causes excessive aeration and should be avoided.
5. 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.
6. 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.

1. Solids are finely powdered are passed through a sieve (# 250, # 180, #125).
2. 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.
3. Finally liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment and thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Example:

1. 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.I2, KI.2I2, KI.3I2 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.

1. 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

Procedure:

1. KI is dissolved in water. I2 is dissolved in it.
2. Woolfat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 400C.
3. I2 solution is added to the melted mass in small quantities at a time with continuos stirring until a uniform mass is obtained.
4. It is cooled to room temperature and packed.

Use: - Ringworm in cattle.

**(b) Ointment containing combined iodine**

Fixed oils and many vegetable and animal fats absorb iodine which combines with the double bonds of the unsaturated constituents, e.g.

CH3.(CH2) 2.CH = CH.(CH2) 7.COOH + I2 → CH3.(CH2) 2.CHI CHI.(CH2) 7.COOH

 Oleic acid di-iodostearic acid

Example: Non-staining Iodine Ointment B.P.C. 1968

 Iodine

 Arachis Oil

 Yellow Soft Paraffin

Method:

1. Iodine is finely powdered in a glass mortar and required amount is added to the oil in a glass-stoppered conical flask and stirred well.
2. The oil is heated at 500C in a water-bath and stirred continually. Heating is continued until the brown color is changed to greenish-black; this may take several hours.
3. From 0.1g of the preparation the amount of iodine is determined by B.P.C. method and the amount of soft paraffin base is calculated to give the product the required strength.
4. Soft paraffin is warmed to 400C. The iodized oil is added and mixed well. No more heat is applied because this causes deposition of a resinous substance.
5. The preparation is packed in a warm, wide-mouthed, amber color, glass bottle. It is allowed to cool without further stirring.

**4. Preparation of ointments by emulsification:**

An emulsion system contain an oil phase, an aqueous phase and an emulsifying agent.

For o/w emulsion systems the following emulsifying agents are used:

 (i) water soluble soap

 (ii) cetyl alcohol

 (iii)glyceryl monostearate

 (iv) combination of emulsifiers: triethanolamine stearate + cetyl alcohol

 (v) non-ionic emulsifiers: glyceryl monostearate, glyceryl monooelate, propylene glycol stearate

For w/o emulsion creams the following emulsifiers are used:

 (i) polyvalent ions e.g magnesium, calcium and aluminium are used.

 (ii) combination of emulsifiers: beeswax + divalent calcium ion

The viscosity of this type of creams prevent coalescence of the emulsified phases and helps in stabilizing the emulsion.

Example:

Cold cream:

Procedure:

1. Water immiscible components e.g. oils, fats, waxes are melted together over water bath (700C).
2. Aqueous solution of all heat stable, water soluble components are heated (700C).
3. Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained.

N.B. The aqueous phase is heated otherwise high melting point fats and waxes will immediately solidify on addition of cold aqueous solution.

**MANUFACTURE OF OINTMENTS / CREAMS IN INDUSTRIAL SCALE**

**1. Preparation of oil and aqueous phase**

Oils + Fats Water soluble ingredients + Purified water

 ↓ Equipment: Steam jacketed kettle ↓ Equipment: Mechanicalstirrer

 Melted and mixed Dissolved

 ↓ ↓

 Strained through several layers of cheese Filtered

cloths to remove foreign matter ↓

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 70–720C for proper mixing.

Three methods of mixing are there:

|  |  |  |
| --- | --- | --- |
| (A) Simultaneous blending * For continuous or large batch operation
* Equipments

Proportioning pumpContinuous 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 450C.

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

Cooled to 43 to 450C

 ↓ 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.

**Evaluation of ointments:**

* **Penetration**
* **Rate of release of medicaments**
* **Absorption of medicaments into blood stream**
* **Irritant effect**

**Penetration-** A weighed quantity of ointment is rubbed over skin for a given period of time and unabsorbed ointment is collected and weighed.

The differences in weights represent the amount absorbed.

**Rate of release of medicament**-To assess rate of release of medicament, small amount of the ointment can be placed on the surface of nutrient agar contained in a Petri dish or alternately in a small cup cut in the agar surface. If the medicament is bactericidal the agar plate is previously seeded with a suitable organism like S.aureus. After a suitable period of incubation, the zone of inhibition is measured and correlated with the rate of release.

**Absorption of medicament into blood stream**

The ointment should be evaluated for the rate of absorption of drug into the blood stream. This test can be run in-vivo only.

Definite amount of ointments should be rubbed through the skin. Under standard conditions and medicaments are estimated in the blood plasma or urine.

**Irritant Effect**

The irritant effect can be judged to a certain extent by injecting the ointment into thigh muscles and under the abdominal skin of rats. Reaction are noted at intervals of 24,48,72 and 96 hours. Lesions on cornea, iris, conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicate irritancy to pressing skin.

**Evaluation of gel**:

* **Drug content**
* **Homogeneity of drug content**
* **Measurement of pH**
* **Viscosity**
* **Spreadability**
* **Extrudability**

**Drug content -**1gm of gel was accurately weighed in a 50ml of volumetric flask to which 20ml purified water was added with continuous shaking. Volume was adjusted with a mixture of 10% methanol in water. Absorbance of the solution with the blank was measured at 360nm using UV-spectrophotometer.

**Homogeneity of drug content -**For homogeneity of drug contents, six tubes were taken randomly and assayed for the drug content as stated above.

**Measurement of pH -**The pH of gels were determined by digital pH meter. One gram of gel was dissolved in 100ml of distilled water and stored at 4°C for two hours.

**Viscosity -**Brookfield viscometer is used for determination of viscosity. Gels were filled in jar and spindle was lowered perpendicularly taking care that spindle do not touch bottom of the jar. The spindle was rotated in the gel at increasing shear rates 0.5, 1, 2.5 and 5rpm. At each speed, the corresponding dial reading was noted.

**Spreadability-** A modified apparatus consisting of two glass slides containing gel in between with the lower slide fixed to a wooden plate and the upper one attached to a balance by a hook was used to determine spreadability.

**Extrudability -** A simple method was adopted for determination of extrudability in terms of weight in grams required to extrude a 0.5cm ribbon of gel in 10 seconds from the collapsible tube.

**IN SITU GELS**

* In situ is a Latin phrase which translated literally as ' In position’ .
* In situ gels are drug delivery systems that are in solution form before administration in the body, but once administered, undergo gelation in situ, to form a gel .
* Administration routes for in situ gel: oral, ocular, rectal, vaginal, injectable and intraperitoneal routes.

**Advantages**

* Increased contact time.
* Improved local bioavailability.
* Reduced dose concentration.
* Reduced dosing frequency.
* Improved patient compliance and comfort.
* Its production is less complex and thus lowers the investment and manufacturing cost.

**General method of in situ gel :**

* Weighed quantities of Timolol maleate, Benzalkonium chloride, EDTA and sodium chloride are dissolved in the pH 4 phosphate buffers under aseptic conditions.
* Polyacrylic acid (Carbopol 934p) is slowly added with continuous stirring at a speed of 1,500-2,000 rpm to minimize the formation of the lumps of undispersed mass.
* HEC is added with slow stirring to avoid foam formation. Stirring is continued until a clear dispersion is formed

**Approaches**

There are six approaches for the in situ gel :

1. Temperature-sensitive hydrogels

2. pH-sensitive hydrogels

3. Ion-sensitive hydrogels

4. Enzyme-sensitive hydrogels

5.Light-sensitive hydrogels

6. Dilution-sensitive hydrogels

**Evaluation**

* **pH**
* **Clarity**
* **Texture analysis**
* **Gelling capacity**
* **Gel strength**
* **Rheological studies**
* **Sol-Gel transition temperature**
* **Fourier Transforms Infrared Spectroscopy**
* **Drug content estimation**
* **In vitro drug release studies**
* **Accelerated stability studies**

**Applications**

1. Oral Delivery.
2. Parenteral Delivery
3. Ocular Delivery
4. Vaginal Delivery
5. Dermal and Transdermal Delivery
6. Nasal Delivery

**HYDROGEL**

* Hydrogel is a network of polymer chains that are hydrophilic, water insoluble, sometimes found as a colloidal gel in which water is the dispersion medium.
* Hydrogels are highly absorbent natural or synthetic polymers.
* Hydrogels are crosslinked polymer networks that absorb substantial amounts of aqueous solutions.
* Hydrogels can contain over 99.9% water.
* Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids.
* The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites.
* The high water content of the materials contributes to their biocompatibility.
* These crosslinks provide the network structure and physical integrity.
* These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media.

**Classification Of Hydrogels:**

**Structure**

* Amorphous Hydrogels
* Semi-crystalline Hydrogels
* Hydrogen Bonded Hydrogels

**Charge**

* Neutral Hydrogels
* Anionic Hydrogels
* Cationic Hydrogels
* Ampholytic Hydrogels

**Mechanism of drug release**

* Diffusion Controlled Release Systems
* Swelling Controlled Release Systems
* Chemically Controlled Release Systems
* Environment Responsive Systems

**Method of preparation**

* Homopolymer Hydrogels
* Co-polymer Hydrogels
* Multi Polymer Hydrogels

**Advantages of Hydrogels**

* Hydrogels possess a degree of flexibility very similar to natural tissue, due to their significant water content.
* Entrapment of microbial cells within Hydrogel beads has the advantage of low toxicity.
* Environmentally sensitive Hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
* Timed release of growth factors and other nutrients to ensure proper tissue growth.
* Hydrogels have good transport properties.
* Hydrogels are Biocompatible.
* Hydrogels can be injected.
* Hydrogels are easy to modify.

**Disadvantages of Hydrogels:**

* Hydrogels are expensive.
* Hydrogels causes sensation felt by movement of the maggots.
* Hydrogels causes thrombosis at Anastomosis sites.
* The surgical risk associated with the device implantation and retrieval.
* Hydrogels are non-adherent; they may need to be secured by a secondary dressing.
* Hydrogels used as contact lenses causes lens deposition,hypoxia, dehydration and red eye

 reactions.

* Hydrogels have low mechanical strength
* Difficulty in handling.
* Difficulty in loading.
* Difficulty in Sterilization

**Method Of Preparation Of Hydrogels:**

* Crosslinking
* Isostatic Ultra High Pressure
* Nucleophilic Substitution Reaction
* Using Gelling Agents
* Use Of Irradiation
* Freeze Thawing

**Pharmaceutical Applications Of Hydrogels:**

* Peroral Drug Delivery
* Drug Delivery In The Oral Cavity
* Drug Delivery in the G.I.T
* Ocular Delivery
* Transdermal Delivery
* Subcutaneous Drug Delivery
* Hydrogels To Fix Bone Replacements
* Tissue Engineering
* Protein Drug Delivery
* Topical Drug Delivery

**SUPPOSITORIES**

**Definition:** Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert localized or systemic effects.

They are used to deliver both systemically-acting and locally-acting medications.

**Types:**

* rectal suppository
* vaginal suppository
* urethral suppository
* nasal suppository

**Suppositories Bases:**

**Properties of Ideal suppository base:**

1. Melts at body temperature or dissolves in body fluids.
2. Non-toxic and non-irritant.
3. Compatible with any medicament.
4. Releases any medicament readily.
5. Easily moulded and removed from the mould.
6. Stable to heating above the melting point.
7. Easy to handle.
8. Stable on storage.

**Types of suppositories bases:**

* Cocoa butter and other fatty bases
* Water soluble and dispersible suppositories bases
* Hydrogels
* Glycerinated gelatin

**Preparation of suppositories:**

* Molds:-
	+ Metal device used to get the required shape.
	+ Made up of aluminum , brass, stainless steel, or plastics.
* Calibration of mold:-
	+ It is the adjustment of mold to get suppositories of uniform weight, even though different base are used.
	+ It is done prier to suppositories.
	+ A set of suppositories are prepared using only the base.
	+ The average weight of them is calculated & it is taken as the true weight of suppositories prepared using that mold , which is the capacity of mold.
* Displacement value:-
	+ The volume of suppository from particular mold is uniform but its weight will vary because the density of medicament usually differ from the density of base .
	+ To prepare product accurately , allowance must be made for the change in density of mass due to added medicament
	+ The most convenient way of making this allowance is to use the displacement value-“ the number of part by the weight of medicament that displace the one part by weight of base”

Suppositories are prepared by four methods:-

* Hand molding method
* Compression molding method
* Pour molding method
* Automatic molding method

**(1)Hand molding method**

Hand shaping suppositories is the oldest and the simplest method of preparing this dosage form.

The manipulation requires considerable skills, yet avoids the complications of heat and mold preparation.

Prescribed quantity of grated powder ingredient

Reduce the ingredients to fine powder in mortar

Soften with diluted alcohol and smooth paste is formed

Grated with theobroma oil and kneaded and triturate in the mortar

Kneading and rolling method was done by hands and rolled into balls

Kneaded mass is rolled between fingers into rod shaped

The rods are cut into pieces and then one end point rolled to give a conical shape.

**(2)Compression molding method**

This method of suppository preparation also avoids heat. The suppository mass, such as a mixture of grated theobroma oil and drug, is forced into a mold under pressure, using a wheel-operated press. The mass is forced into mold openings, pressure is released, and the mold removed, opened, and replaced. On a large scale, cold-compression machines are hydraulically operated, water-jacketed for cooling, and screw-fed. Pressure is applied via a piston to compress the mass into mold openings.

* **Advantages:**
* It is a simple method.
* It gives suppositories that are more elegant than hand moulded suppositories.
* In this method sedimentation of solids in the base is prevented.
* Suitable for heat labile medicaments.
* ***Disadvantages:***
* Air entrapment may take place.
* This air may cause weight variation.
* The drug and/or the base may be oxidized by this air.

**(3)Pour molding method**

* Molds should be filled only when they are at room temperature. A cold or frozen mold should never be used because it can cause fractures and fissures throughout the suppository. Each cavity should be filled slowly and carefully ensuring that no air bubbles are entrapped in the cavity. To prevent layering in the suppositories, the pouring process should not be stopped until all the cavities have been filled. Molds should be allowed to set at room temperature. Refrigeration should only be used if the suppository has not congealed after 30 to 40 minutes.
* Aluminum molds usually require lubrication before use. Hard rubber molds may require lubrication. One way is to use a vegetable oil spray. Other lubricants include light mineral oil when water soluble bases are being used and glycerin or propylene glycol when oleaginous bases are being used. Whatever lubricant is used, only a light coating is needed. If too much lubricant is used, the excess will pool in the tip of the suppository cavity.

**(4)Automatic molding method**

* The molding operations(pouring, cooling, and removal) can be performed by machine. All filling, ejecting, and mold-operations are fully automated. The output of a typical rotary machine ranges from 3500 to 6000 suppositories.
* The machine usually made up of chrome-plated brass molds are installed radially in the cooling turn able
* The method of choice for commercial suppository production involves the automated filling of molds or performed shells by a volumetric dosing pump that meters the melt from a jacketed kettle or mixing tank directly into the moldsor shells. Strips of performed shells pass beneath the dosing pump and are filled successively, passed through cooling chambers (to promote solidification), sealed, and then packaged.

### :

**Packing of suppositories:**

* It can be foiled in aluminum ,plastic, paper, tin strip.
* **Modern packing machine:** nearly 8000 suppositories can be wrapped per hour.
* **In packing molding:** In this ,the suppository mass is directly move into the series of molds which are made up of plastic. After cooling , excess mass is trimmed of . By this technique 12,000 to 15,000 suppositories can be produce per hour.
* **Disposable molds:** They are suitable for tropical climate. They are made up of plastic or aluminum .
* **Labeling:** “store in a cool place.” “Not to be taken orally.”

**Evaluation:**

The various evaluation tests for suppositories are

* [Test of appearance](http://www.pharmainfo.net/evaluation-tests-suppositories#Appearance)
* [Test of physical strength](http://www.pharmainfo.net/evaluation-tests-suppositories#physical_strength)
* [Test of dissolution rate](http://www.pharmainfo.net/evaluation-tests-suppositories#Dissolution_rate)
* Test of melting range
* Test of softening time
* Test of uniformity of drug content
* Test of drug uptake

**Test of appearance**

All the suppositories should be uniform in size and shape. They should have elegant appearance. Individual suppositories should be examined for cracks and pits due to entrapment of air in the molten mass.

**Test of physical strength**

In this test, tensile strength of suppositories is measured to assess their ability to withstand the rigors of normal handling.

The apparatus used is called as breaking test apparatus. It consists of a double-wall chamber. Through the walls of the chamber, water is pumped. The inner chamber consist of a disc which holds the suppositories. To this disc, a rod is attached. The other end of the rod consists of another disc on which weights are placed.

**Procedure**

On the first disc the test suppository is placed. On the second disc a 600 g weight is placed. At 1 minute interval, 200 g weights are added till the suppository crumbles. All the weights used are added which gives the tensile strength. Likewise, few more suppositories are tested and the average tensile strength is calculated. Tensile strength indicates the maximum force which the suppository can withstand during production, packing and handling. Large tensile strength indicates less tendency to fracture.

**Test of dissolution rate**

It is the amount of dosage form that gets dissolved in body fluid in unit time. It is a measure of the rate of drug release from the suppository.

Two types of apparatus are available for testing the dissolution rate. They are:

(a) **Suppository dialysis cell** - Lipophilic suppositories are tested using suppository dialysis cell, which is also called as modified flow-through cell.

(b) **Stationary basket** - Rotating paddle apparatus ( USP dissolution test apparatus ). Hydrophilic suppositories are tested using stationary basket - rotating paddle apparatus.

**Test of melting range**

Both macromelting range and micromelting range are determined.

(a) **Macromelting range**

It is a measure of the thermal stability of the suppository.

It is the time taken by the entire suppository to melt in a constant temperature water bath. The test is conducted using the tablet disintegration apparatus. The suppository is immersed in a constant water bath. Finally the melting range is recorded.

(b) **Micromelting range**

The melting range of the fatty base is measured in capillary tubes.

**Test of softening time**

Softening time is the time for which the suppository melts completely at a definite temperature. This test measures the softening time of suppositories which indicates the hardness of the base.

**Method**

The apparatus consists of a cellophane tube tied at the two ends of a condenser. The two ends of the cellophane tube are open. Water is circulated through the condenser at a definite rate. As a result, after some time the upper half of the tube opens wide and the lower half collapses. A suppository is dropped into the water in the condenser. The time period in which the suppository melts completely is noted as the softening time.

**Test of uniformity of drug content**

This test is to assess the uniformity of the mixed suppository mass. Different suppositories are assayed for the drug. All the suppositories should contain the same labelled quantity of the drug.

**Test of drug uptake**

Both in-vitro and in-vivo tests should be conducted to assess the amount of drug absorbed into the systemic circulation.

(a) **In-Vitro test**

The test conditions should be similar to those inside the human body. The dissolution apparatus is used which consists of simulated gastric and simulated intestinal fluids. Definite number of suppositories are placed in the apparatus. Aliquot portions of the dissolution medium are withdrawn at definite intervals of time and drug uptake is measured using a U.V. spectrophotometer.

(b) **In-Vivo test**

This test is carried in animals or human volunteers. The suppository is placed in the intended body cavity. At regular intervals of time, blood samples are collected and the amount of drug present is determined.