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B.Pharm
Sem-1

Subject Name: Pharmaceutics
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Definition: Semi-solid dosage forms are dermatological preparations intended to apply externally on the skin to produce local or systemic effect e.g. ointments, creams, gels and pastes. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity increasing agents, antimicrobial agents, antioxidants, or stabilizing agents. Semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. Novel semisolids are non-greasy since they are made up of water washable bases. Hence, they cause less irritation to skin and are superior to conventional semisolid dosage form.

5.2 IDEAL PROPERTIES OF SEMI-SOLID DOSAGE FORMS

1. Physical Properties

(a) They should have smooth texture.

(b) They should be elegant in appearance.

(c) They should be non-dehydrating.

(d) They should be non-gritty in nature.

(e) Semi-solid dosage forms possess non-greasy and non-staining property.

(f) They are non-hygroscopic in nature.

2. **Physiological Properties**
   (a) They should be non-irritating.
   (b) They should not alter skin functioning.
   (c) They should be easily miscible with skin secretion.
   (d) They should have low sensitization effect.
3. **Application Properties**
   (a) They should be easily applicable with efficient drug release.
   (b) They should possess high aqueous washability.

5.3 CLASSIFICATION

Types of Semi-solid dosage form

1. Ointments
2. Creams
3. Pastes
4. Gel
5. Poultices
6. Plasters

Ointments: Ointments are semisolid preparations meant for external application to the skin or mucous membrane. They usually contain a medicament or medicaments dissolves, suspended or emulsified in the base.

Creams: Creams are viscous emulsions of semisolid consistency intended for application to the skin or mucous membrane and **o/w** type and **w/o** type.

Pastes: Pastes are the preparations which contains a large amount of finely powdered solids such as starch and zinc oxide. These are generally very thick and stiff.

Jellies: These are thin transparent or translucent, non-greasy preparations. They are similar to mucilages because they are prepared by using gums but they differ from mucilages in having jelly like consistency.

Gels: These are jelly-like semisolid dispersions of drug meant to be applied on the skin.

Suppositories: These are meant for insertion in to the body cavities other than mouth. They may be inserted in to rectum, vagina or urethra.

Poultices: These are also known as cataplasms. They are soft viscous wet masses of solid substances.

Plasters: These are semi-solid masses applied to the skin to enable prolonged contact of drug with the skin. or Substances intended for external application, made of such materials and consistency as to adhere to the skin and thereby attach as dressing.

Mechanism of Skin Permeation

The skin itself has two main layers, the epidermis, which is the outermost layer of the skin, covering the dermis that is the active part of the skin, holding the hair muscles, blood supply, sebaceous glands, and nerve receptors. There is a fat layer underneath the dermis. The skin is a very heterogeneous membrane and has a variety of cell types, but the layer that

controls the penetration of drugs is called the stratum corneum and, despite its thickness of only 15–20 µm, it provides a very effective barrier to penetration. The permeation of the drug through the skin has several routes: transcellular, intercellular, and appendageal (through eccrine (sweat) glands or hair follicles) (Fig. 5.1).

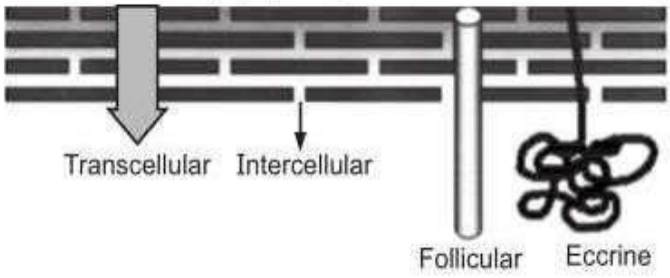

Fig. 5.1: Schematic representation of the different possible routes of penetration through the skin.

Since, the appendages occupy a very low surface area, this means of permeation is less significant under normal conditions. Nevertheless, in iontophoretic delivery this route is more significant. The intercellular spaces consists of a mixture of lipids–ceramides, free fatty acids and their esters, and cholesterol and its sulphates that are structured in bilayers. Recent developments in spectroscopic techniques give interesting insights at the molecular level that may explain the impermeability of the skin by repeated partition and diffusion across structured bilayers. Transdermal drug permeability is influenced mainly by three factors: the mobility of the drug in the vehicle, the release of the drug from the vehicle, and drug permeation through skin. Therefore, the researchers are challenged to come up with formulations that increase the permeability of the drug without irreversibly changing the skin barrier function. Various potential mechanisms to enhance drug penetration through the skin include directly affecting the skin and modifying the formulation so the partition, diffusion, or solubility are altered. Here we will present briefly these potential mechanisms that are interconnected with each other.

1. Direct Effect on the Skin

(a) Denaturation of intracellular keratin or modification of its conformation causes swelling and increased hydration.

(b) Affection of desmosomes (known as macula adherens- cell structures specialized for cell to cell adhesion) that maintain cohesion between corneocytes (dead cells of the stratum corneum).

(c) Modification of lipid bilayers reduces resistance to penetration.

(d) Altering the solvent properties of the stratum corneum to modify drug partitioning.

(e) Use of solvent that can extract the lipids in the stratum corneum and decrease its resistance to penetration.

2. Modification of the Formulation

(a) Super saturation state produced by volatile solvent that leaves the active substance in a more thermodynamically active state.

(b) Choosing the enhancer molecules in the vehicle that are good solvents for the active ingredient and which enhance permeation through the skin; this way the partition of the drug into the stratum corneum will be improved.

(c) The diffusion of the active ingredient through the skin may be facilitated by using enhancers that create liquid pools within the bilayers like oleic acid, or disturb the bilayers uniformly as do the Azone® molecules (1-dodecyl azacyclo heptan-2-one or lauro capram) is the first molecule specifically designed as a skin permeation enhancer. Azone® serves as surfactant and enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents.

5.4 FACTORS INFLUENCING DERMAL PENETRATION OF DRUGS

5.4.1 Physiological and Pathological Condition of Skin

(a) Reservoir effect 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.

(b) 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.

(c) Skin hydration: 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.

(d) Skin age: The young skin is more permeable than older. Childrens are more sensitive for skin absorption of toxins. Thus, skin age is one of the factors affecting penetration of drug.

(e) Blood flow: Changes in peripheral circulation can affect transdermal absorption.

(f) Skin temperature: The permeation of drug increase ten folds with temperature variation. The diffusion coefficient decreases as temperature falls. Weak acids and weak bases dissociate depending on the pH and pKa or pKb values. The proportion of unionized drug determines the drug concentration in skin. Thus, temperature and pH are important factors affecting drug penetration.

(g) Regional skin site: Thickness of skin, nature of stratum corneum and density of appendages vary site to site. These factors affect significantly penetration.

(h) Species variation: The skin thickness, density of appendages and keratinization of skin vary species to species, so affects the penetration.

(i) Skin metabolism: Skin metabolizes steroids, hormones, chemical carcinogens and some drugs. So skin metabolism determines efficacy of drug permeated through the skin.

5.4.2 Physico-Chemical Properties of Active Substances

(a) **Molecular characteristic of drug:** Molecular weight upto 400 daltons can easily penetrate through the skin surface.

(b) **Drug concentration:** The flux is proportional to the concentration gradient across the barrier and concentration gradient will be higher if the concentration of drug will be more across the barrier.

(c) **Solubility and partition coefficient:** Highly lipid soluble molecules enters through hair follicles. Moderately lipid soluble molecules penetrates directly across the horny layer.

(d) **Crystal structure/polymorphism:** 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.

(e) **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.

(f) **Partition coefficient:** The optimal partition coefficient (K) is required for good action.
Drugs with high K are not ready to leave the lipid portion of skin. Also, drugs with low K will not be permeated.

(g) **Diffusion coefficient:** Penetration of drug depends on diffusion coefficient of drug. At a constant temperature the diffusion coefficient of drug depends on properties of drug, diffusion medium and interaction between them.

5.4.3 Effects of Vehicles

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.

5.4.4 Effects of Additives

(a) Surfactants increases the penetration because they are surface active agents which reduces the surface tension e.g., quaternary ammonium compounds, alkali soaps etc

(b) Humectants increases the solubility of active ingredients. To elevate its skin preparation and to elevate the hydration of the skin e.g., glycerine, polyethylene glycol etc.

(c) Penetration enhancers- Penetration can be improved by addition of penetration enhancers like methanol, oleic acid etc.

Classification of Semi-solid Bases and their Selection

There are four classes or types of bases which are differentiated on the basis of their physical composition.

These are:

1. Oleaginous bases
2. Absorption bases
3. Emulsifying base (Water in oil emulsion bases and Oil in water emulsion bases)
4. Water soluble bases

1. Oleaginous Bases

These bases are fats, fixed oils, hydrocarbon or silicones. They are anhydrous, non-washable, does not absorb water. They should not be applied to infected skin. They are used as protectants, emollients, vehicles for hydrolysable drugs. Examples: White Petrolatum, White Ointment.

2. Absorption Bases

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 are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantities of water but still retaining their ointment-like consistency.

The absorption bases are of two types: i) Non-emulsified bases ii) Water in oil emulsion bases.

The non-emulsified bases absorb water and aqueous solution producing w/o emulsion e.g. Wool fat, wool alcohol, bees wax and cholesterol.

The water in oil emulsion is capable of absorbing more water and have the properties of non-emulsified bases. Example: Hydrous wool fat (lanolin).

3. Emulsifying Bases

These are anhydrous, hydrophilic, absorbs water and non-water removable, with low thermal conductivity and occlusive. They have the same properties as the absorption bases. They are used as emollients, cleansing creams, vehicles for solid, liquid, or non-hydrolyzable drugs. Examples: Cold Cream type, Hydrous Lanolin, Rose Water Ointment, Hydrocream, Nivea.

Oil in water emulsion bases

These bases are anhydrous, water soluble, absorb water and water washable. They are either Carbowaxes Polyethylene Glycols (PEGs) or hydrated gums (Bentonite, gelatin, cellulose derivatives). They are used as drug vehicles. Examples: PEG Ointment, Polybase™.

4. Water Soluble Bases

Water soluble does not contain oily substances and are called greaseless base and are completely soluble in water. Examples:

(A) Polyethylene glycol (PEGs), polyoxyl 40 stearate and polysorbates.

(B) Macrogols: They are mixture of water and polycondensation products of ethylene oxide.

They are of three types. (i) Solid Macrogols (ii) Liquid Macrogols (iii) Semisolid Macrogols.

Advantages

(a) They are water soluble and washable.

(b) They are non-greasy, non-staining, non or less occlusive, lipid free in nature.

(c) They are relatively inert.

(d) They do not allow mould growth.

Disadvantages

They may dehydrate skin and hinder percutaneous absorption.

Selection of the appropriate base based on:

1. Dermatological factors
2. Pharmaceutical factors

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 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 serum: 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. Lard which is obtained from animal origin rancify rapidly due to oxidation and gives bad odour. This type of reactions are called rancidification. 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 (Vitamin 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.

5.5 METHODS OF PREPARATION

1. Trituration method
2. Fusion method
3. Emulsification Method:
   (a) Preparation of oil and aqueous phases
   (b) Mixing of the phases
   (c) Cooling the emulsion
   (d) Homogenization
4. Chemical reaction method.

1. **Trituration Method:** It is the most commonly used for the preparation of semisolid. When base contains soft fats and oils, or medicament is insoluble or liquid, then this method is used with spatula or motar and pestle.

2. **Fusion Method:** The ingredients of the base are melted together and properly mixed to obtain a uniform product. Initially, the ingredient of high melting point is melted. Then remaining ingredient of the base are added in the decreasing order of their melting points and melted with constant stirring. The above mixture is removed from the water bath and stirred in order to cool it. If the drug is soluble in the base, then its powdered form is added to the molten base. Liquid or semisolid are added at a temperature of 40°C. Insoluble additives are added in small quantities with proper stirring, when the thickening of the base starts. Localized cooling of the molten base and vigorous stirring should be avoided to prevent aeration of the ointment.

3. **Emulsification Method**

Preparation of Oil and Aqueous Phases: Place the ingredients of the oil phase into the stainless steel steam-jacketed kettle and melt them whilst mixing. Filter the oil phase through several layers of cheese cloth to remove any foreign matter. Heat the emulsion mixing kettle to the temperature of the oil phase. This avoids congealing of higher melting component. Transfer the oil phase into the emulsion mixing kettle. Dissolve the ingredient of the aqueous phase in purified water and filter the solution. A soluble drug which is thermostable may be added to the aqueous phase in this step.

The phases are usually mixed at a temperature of 70 to 72°C, because at this temperature intimate mixing of the liquid phases can occur. The properties of some emulsions depend on the temperature at which the phases are mixed.

Three ways of mixing the phases: 1. Simultaneous blending of the phases. 2. Addition of the discontinuous phase to the continuous phase. 3. Addition of the continuous phase to the discontinuous phase.

Equipments used for mixing of phases:

Agitator mixers: Sigma mixer and planetary mixer.

Shear mixers: Triple roller mill and Colloidal mill.

4. **Chemical reaction:** This method is used to prepare several types of ointments. This method involves both fusion and mechanical mixing. Best example of this method is Iodine ointment.

Chemical Reaction Method Procedure for iodine ointment: Powder iodine in a mortar and pestle and add it to arachis oil taken in a flask. Heat the mixture to 50°C with occasional stirring until greenish black colour appears. Add yellow soft paraffin to the above mixture and heat it to 40°C with mixing. Cool the Ointment.

5.6 PREPARATION OF OINTMENTS

An ointment should be:

(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.

5.6.1 Ointments Prepared by Fusion Method

When an ointment base contain a number of solid ingredients such as white bees wax, cetyl alcohol, stearyl alcohol, stearic acid, hard paraffin, etc. as components of the base, it is required to melt 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.

Advantage

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

Method-II

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

Advantage

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. bees wax, 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 discolours due to oxidation e.g. wool fats and wool alcohols and this discoloured 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	-	50 g
Hard paraffin	-	50 g
Cetostearyl alcohol	-	50 g
White soft paraffin	-	850 g

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.

5.6.2 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.

Examples

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

Formula:

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

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) Sulphur ointment I.P.

Sublimed sulphur – 10 g

Simple ointment – 90 g

Prepare an ointment.

Method: Sublimed sulphur is sieved through no. 180 sieves. Then sublimed sulphur is triturated with small amount of simple ointment. Then the remaining amount of simple ointment is added and the mixture is levigated until smooth and homogenous mass is obtained.

5.6.3 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.

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

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

Example, **Strong Iodine Ointment** (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 colour. Due to improper storage the water dries up and the iodine crystals irritate the skin, hence glycerol is some times added to dissolve the iodine-potassium iodide complex instead of water.

Example: Strong Iodine Ointment.

Iodine – 4 g
Woolfat - 4 g
Yellow soft paraffin – 76 g
Potassium iodide – 4 g
Water – 12 g

Procedure

(i) KI is dissolved in water. I_2 is dissolved in it.
(ii) Wool fat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 40°C.
(iii) I_2 solution is added to the melted mass in small quantities at a time with continuous stirring until a uniform mass is obtained.
(iv) 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.

$$CH_3{\cdot}(CH_2)_2{\cdot}CH = CH{\cdot}(CH_2)_7{\cdot}COOH + I_2 \quad CH_3{\cdot}(CH_2)_2{\cdot}CHI\ CHI{\cdot}(CH_2)_7{\cdot}COOH$$

Oleic acid — Di-iodostearic acid

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

Iodine – 5 g
Arachis oil – 15 ml
Yellow soft paraffin - q.s. to 100 g

Method

(a) 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.
(b) The oil is heated at 50°C in a water-bath and stirred continually. Heating is continued until the brown colour is changed to greenish-black; this may take several hours.
(c) From 0.1 g 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.
(d) Soft paraffin is warmed to 40°C. The iodized oil is added and mixed well. No more heat is applied because this causes deposition of a resinous substance.
(e) The preparation is packed in a warm, wide-mouthed, amber colour, glass bottle. It is allowed to cool without further stirring.

5.6.4 Preparation of Ointments/Cream 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: *bees wax + 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

(i) Water immiscible components e.g. oils, fats, waxes are melted together over water bath (70°C).
(ii) Aqueous solution of all heat stable, water soluble components are heated (70°C).
(iii) Aqueous solution is slowly added to the melted bases with continuous stirring until the product cools down and a semi-solid mass is obtained.

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

5.7 PASTE

Pastes are semisolid preparations for external application 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. They do not melt at ordinary temperature they form a coating over the affected area. Pastes are used as protective, antiseptic, and soothing dressings.

5.7.1 Differences Between Pastes and Ointments

(i) Pastes generally contains a large amount (50%) of finely powdered solids. So they are often stiffer than ointments.
(ii) When applied to the skin pastes adhere well, forming a thick coating protects and soothes inflamed and raw surfaces and minimizes the damage done by scratching in itchy conditions such as chronic eczema. It is comparatively easy to confine pastes to the diseased areas whereas ointments, which are usually less viscous, tend to spread on to healthy skin, and this may result in sensitivity reactions if the preparations contain a powerful medicament such as dithranol.

(iii) Because of the powder contents pastes are porous; hence, perspiration can escape. Since, the powders absorbs exudate, pastes with hydrocarbon base are less macerating than ointments with a similar base.

(iv) They are less greasy than ointments but since their efficacy depends on maintaining a thick surface layer they are far from attractive cosmetically.

(v) Most of the pastes are unsuitable for treating scalp conditions because they are difficult to remove from the hair.

5.7.2 Methods of Preparation

Like ointment, pastes are prepared by trituration and fusion methods. Trituration method is used when the base is liquid or semisolid.

Fusion method is used when the base is semisolid and/or solid in nature.

Preparation 1.

Name: Compound Zinc Paste

Formula:

Zinc oxide, finely sifted	-	25 g
Starch, finely sifted	-	25 g
White soft paraffin	-	50 g

Type of preparation: Paste with semi-solid base prepared by fusion and trituration.

Procedure

(a) Zinc oxide and starch powder are passed through No. 180 sieve.

(b) Soft paraffin is melted on a water bath.

(c) The required amount of powder is taken in a warm mortar, triturated with little melted base until smooth. Gradually rest of the base is added and mixed until cold.

Preparation 2.

Name: Zinc and Coal tar Paste B.P.C.

Formula: Zinc oxide, finely sifted - 60 g
Coal tar- 60 g
Emulsifying wax – 50 g
Starch- 380 g
Yellow soft paraffin – 450 g

Type of preparation: Paste with semi-solid base prepared by fusion.

Procedure

Method-I

(a) Emulsifying wax is melted in a tarred dish (70°C).

(b) The coal tar is weighed in the dish. Stirred to mix.

Soft paraffin is melted in a separate dish (70°C) and about half is added to the tar-wax mixture; stirred well. Remainder is added; stirred again until homogeneous.

Allowed to cool at about (30°C) and zinc oxide (previously passed through 180 mesh) and starch, in small amount with constant stirring. Stirred until cold.

Method-II

Wax and paraffin melted together, mixed well and stirred until just setting. Powders are mixed on a slightly warm tile and the tar is incorporated. This method eliminates the risk of over heating.

5.8 GELS

Gels are transparent semisolid preparation meant for external application to the skin or mucous membrane. Gels are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules in an liquid vehicle appear jelly like by the addition of a gelling agent.

These are organic hydrocolloids or hydrophilic inorganic substances.

They contains Tragacanth, Sodium Alginate, Pectin, Starch, Gelatin, Cellulose Derivatives, Carbomer, and Poly Vinyl Alcohol Clays. These are numerous gelling agents varying in gelling ability.

Clear gels are microemulsions in which the diameter of the dispersed phase globules is in the range of 10 to 60 nm. These emulsions are thermodynamically stable. Microemulsions are transparent as the globule diameter of the disperse phase is less than the wavelength of light.

Microemulsions can be distinguished from other types of gels by the vibrations or 'ringing' that occurs when the emulsion is subjected to impact.

Procedure of Clear Gel

- Gel is prepared by mixing a suitable thickening agent with an aqueous vehicle.
- The drug is dissolved in an aqueous vehicle and the thickening is added by triturating in a mortar.
- The trituration is carried out until a homogenous preparation is formed.

Ingredient: Quantity for 50 gm –

Sodium Carboxy methyl cellulose (thickening agent) - 2.5 gm

Glycerol (binding agent) - 1.5 gm

Preservative - 0.05 gm

Colour - 0.0005 gm

Purified water (vehicle)

To make - 50 gm

Method: Dissolved methyl paraben in water by heating. Add SCMC to glycerine and stir thoroughly. Add this mixture to the aqueous vehicle and stir in a uniform, homogenous preparation is formed. Add the dye colour and stir. Transfer to a suitable container.

Evaluation of Gel

The various evaluation parameters involved the assessment of the properties of the gels are be as follows:

1. **Yield Value:** It is a measure of the force required to extrude the material from the deformable bottle tube. It can be determined by the use of an instrument called the Penetrometer. Penetrometer consist of a metal needle that pierces through the system and the distance of penetration of the needle is measured, from which the yield value may be calculated.
2. **Spreadability:** The Spreadability test is performed to determine the extent of Spreadability of gels based on their rheological properties.
3. **Stability:** This test is known as the shipping test and is performed to determine the extent of stability of gels at varying temperature, which the product may experience while exporting to other countries.

5.9 EXCIPIENTS USED IN SEMISOLID DOSAGE FORMS

1. **API:** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Active pharmaceutical ingredient is any part of drug which produces any effect.
2. **Preservatives:** 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. 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.
3. **Humectants:** such as, glycerin, propylene glycol and sorbitol may be added to prevent the loss of moisture from the preparation.
4. **Emulsifying agents:** Like polysorbate, anionic emulsifying agents etc. are added if required.
5. **Antioxidant:** 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.
6. **Organoleptic agents:** suitable colouring agent – (amaranth, brilliant blue etc.) flavouring agent (vanilla , strawberry, raspberry) are added.

   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.

5.10 EVALUATION OF SEMI-SOLID DOSAGE FORMS

1. **Content uniformity of drug:** A known weight of ointment is taken and assayed for amount of the drug.
2. **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.
3. **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. 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.
4. **Absorption of medicament into blood stream:** 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.
5. **Irritant effect:** In general no ointment should possess irritant effect on the skin or mucous membranes the tests for irritancy can be carried out on the skin and eyes of rabbits or the skin of human beings. The irritant effect can also 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.
6. **Consistency test:** Using penetrometry.

Procedure

Preparation of test sample: Three methods (A, B, C).

A: Carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

B: Apply a suitable shear to the samples for 5 minutes carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

C: Melt three samples carefully and completely fill three containers without forming air bubbles. Level it if necessary to obtain a flat surface.

Determination of Penetration

Place the test sample on the basis of the penetrometer. Verify that its surface is perpendicular to the vertical axis of the penetrating object. Bring the temperature of the penetrating object to 25 ± 0.5°C and then adjust its position such that its tip just touches the surface of the sample. Release the penetrating object and hold it free for 5 sec. Clamp the penetrating object and measure the depth of penetration. Repeat the test with two remaining containers.

1. **Rheology:** The rheology or viscosity should remain constant. As creams are normally non-Newtonian in nature, the viscosity can be measured using viscometers used for such liquids. Rheologic measurements are utilized to characterize the ease of pouring from a bottle, squeezing from a tube, maintaining product shape in a jar etc.
2. **Sensitivity:** As various types of ingredients are used with occasional use of antiseptics hormones etc. there is a possibility of sensitization or photosensitization of the skin. This test is normally done by patch test. The test sample is applied along with a standard market product at different places and effect is compared after a period of time.

5.11 IN-SITU GEL

It is a drug delivery system which is in a solution form before the administration in the body but it converts in to a gel form after the administration.

There are various routes such as oral, ocular, vaginal, rectal, intravenous, intraperitoneal etc.

Advantages

- They have ease of administration.
- In-situ gel shows improved local bioavailability.
- They possess reduced dose concentration and reduced dosing frequency.
- It allows improved patient compliance and comfort.
- It can be administered by unconscious patients.
- Drug gets released in a sustained and controlled manner.
- Natural polymers have inherent properties of biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities.
- Synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality.
- In-situ gels can also be engineered to exhibit bioadhesiveness to facilitate drug targeting, especially through mucous membranes, for non-invasive drug administration.
- In-situ gels offer an important "stealth" characteristic in-vivo, owing to their hydrophilicity which increases the in-vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities.
- Simple formulation and manufacturing so less investment and cost.

5.12 IMPORTANCE OF IN-SITU GELLING SYSTEM

- The major importance is the possibilities of administrating accurate and reproducible quantities compared to already formed gel.
- In-situ forming polymeric delivery system such as ease of administration and reduced frequency of administration improved patient compliance and comfort.

- Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye and undergoes a sol-gel transition from instilled dose.
- Liquid dosage form that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

Note

- The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation from which the drug gets released in a sustained and controlled manner.
- Various biodegradable polymers that are used for the formation of in-situ gels include pectin, guar gum, carbopol, xyloglucan, gellan gum, alginic acid, xanthum gum, chitosan, hydroxy propyl methyl cellulose (HPMC), poloxamer etc. Mainly in-situ gel administered by oral ocular, rectal, vaginal, injectable and intaperitoneal routes.

Ideal characteristics of polymers for preparation of in-situ gels

1. It should be biocompatible.
2. It is capable of adhering to the mucous membrane.
3. Preferred pseudo plastic behaviour of polymer.
4. Good tolerance and optical clarity is more preferred.
5. It should influence the tear behaviour.
6. The polymer should be capable of decreasing the viscosity with increasing shear rate.

Mechanism of in-situ gels

In-situ formation based on physical mechanism:

1. **Swelling:** In-situ formation may also occur when material absorbs water from surrounding environment and expand to desired space. One such substance is myverol (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in-vivo by enzymatic action.
2. **Diffusion:** This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system. In-situ formation based on chemical reactions mechanism Chemical reactions that results in-situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes

Applicability of in-situ polymeric drug delivery system

- Used in oral drug delivery system.
- Used in ocular drug delivery.
- Used in nasal drug delivery.
- Used in rectal drug delivery system.
- Used in injectable drug delivery system for dermal and transdermal drug.

Evaluation of in-situ gel:

- **Test for Clarity test:** The clarity of formulated solution is determined by visual inspection under black and white background.
- **Texture analysis:** The consistency, firmness and cohesiveness of in-situ gel are assessed by using texture profile analyzer which mainly indicated gel strength and easiness in administration in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with mucous surface.
- **Determination of pH:** pH can be determined formulation is taken in beaker and 1 ml sodium hydroxide is added drop wise with continuous stirring. pH is checked by using pH meter.
- **Gelling capacity:** In-situ gel is mix with simulated tear fluid (in the proportion of 25 : 7 i.e. application volume 25 µl and normal volume of tear fluid in eye is 7 µl) to find out gelling capacity of ophthalmic product. The gelation assessed visually by noting the time for and time taken for dissolution of the formed gel.
- **Rheological studies:** The viscosity measured by using Brookfield viscometer, cone & plate viscometer. In-situ gel formulation is placed in sample tube. Formulation should have viscosity 5-1000 mPas, before gelling and after ion gel activation by eye will have viscosity of from about 50-50,000 mPas.
- **In-vitro drug release studies:** In-vitro release study of insitu gel solution is carried out by using Franz diffusion cell. The best fit model is check for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics.
- **Sterility testing:** Sterility testing is carried out as per the IP 1996. The formulation is incubated for not less than 14 days at 300- 350°C in the fluid thioglycolate medium to find the growth of bacteria and at 200-250°C in Soya bean casein digest medium to find the growth of fungi in formulation.
- **Isotonicity evaluation:** Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. All ophthalmic preparations are subjected to isotonicity testing, since they exhibited good release characteristics and gelling capacity and the requisite viscosity.