Course… … .. D. Pharm 2nd year

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Unit… … … … . 5

Topic… … … . Semi solid dosage forms

Ointments
a smooth oily substance that is rubbed on the skin for medicinal purposes or as a cosmetic.

Types of ointments

Various types of ointments are:

1.Unmedicated ointments
2. Medicated ointments

Unmedicated ointments

These ointments do not contain any drugs. They are useful as emollients , protectants.
e.g…Petroleum jelly.

Medicated ointments

These ointments contain drugs which show local or systemic effects.

These are of several sub-types:

1.Dermatological ointments
2.Opthalmic ointments
3.Rectal ointments
4.Vaginal ointments
5.Nasal ointments

Advantages

1.Handling of ointments is easier than bulky liquid dosage form.
2.They are chemically more stable than liquid dosage forms.
3.They facilitate application of the directly to the effected body part and avoid exposure of other parts to the drug.

4.They are suitable for patients who find it difficult to take the drugs by parenteral and oral routes.
5.They prolong the contact time between the drug and effected area.
6.The bioavailability of drugs administered as ointments is more since it prevents passage through liver.

Disadvantages

1.They are bulkier than solid dosage forms.
2.When applications of an exact quantity of ointment to the affected area is required , it is difficult to ascertain the same.
3.They are less stable than solid dosage form.

Ointment Applications

There are various parts of the body surfaces, skin and mucous membranes where ointment is applied for curing certain skin or disease conditions. Ointment is applied on hands, legs, face, eyes, ears, vagina, anus, throat etc. There are various problems when an ointment is suggested for treatment such as

Ointment for burns
Ointments for cuts
Ointments for pain
Ointments for itching
Ointments for inflammation and pain
Ointments for boils and scars
Ointments for skin problems like eczema, dermatitis and psoriasis.

List of Ointments

An ointment may or may not be medicated. Some are easily over the counter while are some are prescribed by the doctor. Since they are very moisturizing, they are good for dry skin. Ointments also have a low risk of sensitization and low irritation risk. There is typically little difference between brands of generics and name brand drugs. Some popular ointments are listed below:

Betamethasone
Clotrimazole Cream
Norfloxacin
Soframycin
Ciprofloxacin
Ketoconazole
Ofloxacin

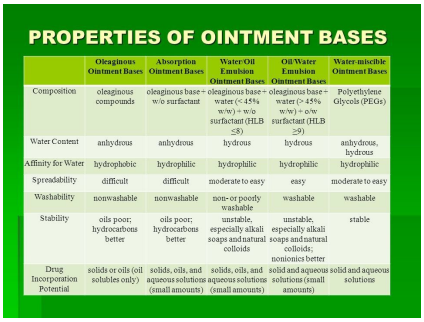
Tobramycin + Dexamethasone
Povidone-Iodine
Diclofenac
Polymyxin-B

Ointment Bases

There are five (5) classes or types of ointment bases which are differentiated on the basis of their physical composition. These are:

oleaginous bases
absorption bases
water in oil emulsion bases
oil in water emulsion bases
water soluble or water miscible bases

Each ointment base type has different physical characteristics and therapeutic uses based upon the nature of its components. The following table summarizes the composition, properties, and common uses of each of the five types



PROPERTIES OF OINTMENT BASES

	Oleaginous Ointment Bases	Absorption Ointment Bases	Water/Oil Emulsion Ointment Bases	Oil/Water Emulsion Ointment Bases	Water-miscible Ointment Bases
Composition	oleaginous compounds	oleaginous base + w/o surfactant	oleaginous base + water (~15% w/w) + w/o surfactant (HLB ≤8)	oleaginous base + water (>45% w/w) + o/w surfactant (HLB ≥9)	Polyethylene Glycols (PEGs)
Water Content	anhydrous	anhydrous	hydrous	hydrous	anhydrous, hydrous
Affinity for Water	hydrophobic	hydrophilic	hydrophilic	hydrophilic	hydrophilic
Spreadability	difficult	difficult	moderate to easy	easy	moderate to easy
Washability	nonwashable	nonwashable	non- or poorly washable	washable	washable
Stability	oils poor; hydrocarbons better	oils poor; hydrocarbons better	unstable, especially alkali soaps and natural colloids	unstable, especially alkali soaps and natural colloids; nonionics better	stable
Drug Incorporation Potential	solids or oils (oil solubles only)	solids, oils, and aqueous solutions (small amounts)	solids, oils, and aqueous solutions (small amounts)	solid and aqueous solutions (small amounts)	solid and aqueous solutions

Preparation of ointments

A well-made ointment is -

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

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

Two mixing techniques are frequently used in making ointments:

1. Fusion, in which ingredients are melted together and stirred to ensure homogeneity.

2. Trituration, in which finely-subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base or one of its ingredients followed by dilution with gradually increasing amounts of the base.

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

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

Method-I

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

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

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

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

Cautions:
(i) Melting time is shortened by grating waxy components (i.e. beeswax, wool alcohols, hard-paraffin, higher fatty alcohols and emulsifying waxes) by stirring during melting and by lowering the dish as far as possible into the water bath so that the maximum surface area is heated.
(ii) The surface of some ingredients discolors due to oxidation e.g. wool fats and wool alcohols and this discolored layers should be removed before use.
(iii) After melting, the ingredients should be stirred until the ointment is cool, taking care not to cause localized cooling, e.g. by using a cold spatula or stirrer, placing the dish on a cold surface (e.g. a plastic bench top) or transferring to a cold container before the ointment has fully set. If these precautions are ignored, hard lumps may separate.

(iv) Vigorous-stirring, after the ointment has begun to thicken, causes excessive aeration and should be avoided.
(v) Because of their greasy nature, many constituents of ointment bases pickup dirt during storage, which can be seen after melting. This is removed from the melt by allowing it to sediment and decanting the supernatant, or by passage through muslin supported by a warm strainer. In both instances the clarified liquid is collected in another hot basin.
(vi) If the product is granular after cooling, due to separation of high m.p. constituents, it should be remelted, using the minimum of heat, and again stirred and cooled.

Example:

(i) Simple ointment B.P. contains

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

Type of preparation: Absorption ointment base

Procedure:

Hard paraffin and cetostearyl alcohol on water-bath. Wool fat and white soft paraffin are mixed and stirred until all the ingredients are melted.

If required decanted or strained and stirred until cold and packed in suitable container.

(ii) Paraffin ointment base

Type of preparation : Hydrocarbon ointment base

(iii) Wool alcohols ointment B.P.

Type of preparation: Absorption base

(iv) Emulsifying ointment B.P.

Type of preparation: Water-miscible ointment base.

(v) Macrogol ointment B.P.C

Type of preparation: Water soluble ointment base

Formula: Macrogol 4000
Liquid Macrogol 300

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

2. **OINTMENT PREPARED BY TRITURATION**

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

(i) Solids are finely powdered are passed through a sieve (# 250, # 180, #125).

(ii) The powder is taken on an ointment-slab and triturated with a small amount of the base. A steel spatula with long, broad blade is used. To this additional quantities of the base are incorporated and triturated until the medicament is mixed with the base.

(iii) Finally liquid ingredients are incorporated. To avoid loss from splashing, a small volume of liquid is poured into a depression in the ointment an thoroughly incorporated before more is added in the same way. Splashing is more easily controlled in a mortar than on a tile.

Example:

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

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

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

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

3. **OINTMENT PREPARATION BY CHEMICAL REACTION**

Chemical reactions were involved in the preparation of several famous ointments of the past, e.g. Strong Mercuric Nitrate Ointment, both 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:

(i) They stain the skin a deep red color.

(ii) Due to improper storage the water dries up and the iodine crystals irritate the skin, hence glycerol was some times 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:

(i) KI is dissolved in water. I2 is dissolved in it.

(ii) Woolfat and yellow soft paraffin are melted together over water bath. Melted mass is cooled to about 400C.

(iii) I2 solution is added to the melted mass in small quantities at a time with continuos 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.

$CH_3.(CH_2)_2.CH = CH.(CH_2)_7.COOH + I_2 \rightarrow CH_3.(CH_2)_2.CHI\ CHI.(CH_2)_7.COOH$

Oleic acid — di-iodostearic acid

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

Yellow Soft Paraffin

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 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.

(c) 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.

(d) 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.

(e) 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:

(i) Water immiscible components e.g. oils, fats, waxes are melted together over water bath (700C).

(ii) Aqueous solution of all heat stable, water soluble components are heated (700C).

(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.

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

Stability of ointments

Storage and dispensing

- Ointments should be stored in tightly closed and completely filled containers
- Changes in temperature can lead to the crystallization of the drug and to changes in the ointment base.
- They are usually dispensed in jars of glass or plastic material or in collapsible tubes.
- Sterile ointments must be dispensed in tubes or single dose units in order to protect the product against contamination during use.
- With tin tubes, there is a risk of corrosion with hydrophilic ointments.

- Continue adding ointment to the jar again using the spatula to put the ointment along the sides of the jar.
- As you fill the jar, stab the spatula into the ointment a couple of times. This will reveal air pockets that may have formed.
- Put the spatula halfway across the filled jar, and tilt in slightly . Rotate the jar and this is make a professional looking finish on the top of the ointment.
- Wipe off ointment from the threads of the jar.
- Cap the ointment jar.

1.Universal Tests:

Description:

This includes visual examination to identify changes in color, separation, crystallization etc., in the final appearance of the product.

The description should specify the content or label claim of the product.

2.Identification:

Quantitative identification of active ingredients in the finished dosage form.

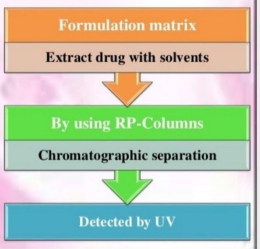
Methods:

- IR
- Raman spectroscopy
- Chromatography

3.ASSAY:

The quantity of drug present in unit weight or volume of ointment or cream is determined by:

- Spectrophotometric method
- Titrimetric method
- Chromatographic method
- Microbial assays



4.MICROBIAL ASSAYS

Microbial assays are recommended for preparations containing antibiotics such as:

- Amphotericin-B
- Bacitracin
- Chlortetracycline HCl
- Gentamycin sulphate

Method:

- Cylindrical plate or plate assays
- Turbidimetric or tube assays

5.IMPURITIES:

The impurities arising from degradation of drug substance and during the manufacturing process of drug product should be assessed and controlled

On 14thday	No.of vegetative cells NMT 0.1% of intial conc
On 28th day	No, of organisms should be below or equal to intial conc

6.PARTICLE SIZE DETERMINATION:

- Dilute preparation with equal volume of glycerol/ liquid paraffin as per monograph.
- Mount on glass slide.
- Observe through microscope.
- Calculate the no. of particles having max., diameter within stated limit.

II.SPECIFIC TESTS:

1.P^{H}

- Creams and ointments contain very limited quantities of water or aqueous phase,
- Hence this test is not always warranted.
- **Formulation dependent.**
- **Not included in compendia drug product monograph.**

2.APPARENT VISCOSITY:

- Formulation and/or process dependent.
- Not included in compendia drug product monograph.

III.SPECIFIC TESTS FOR SEMISOLID DOSAGE FORMS:

1.PHASE SEPARATION TEST:

- Visual tests.
- Done by measuring the volume of separated phases.

2.UNIFORMITY IN CONTAINERS:

Type	Assay Limit
Multiple dose products containing ≥5gm	90-110% of product label
Multiple dose products containing <5gm	90-110% of product label

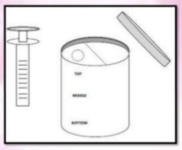
Procedure:

- Expose the product in tube.
- Visually inspect product.
- Remove a sample of product from **top, middle and bottom** portions of the tube.
- Perform assay separately

Products Packaged In Containers Other Than Tubes:

- Select a syringe such that it reaches bottom of the container.
- Remove plunger & cut of bottom of syringe barrel.
- Sample from one side of container is slowly withdrawn by slowly inserting syringe barrel into container until it reaches bottom.

- Twist syringe barrel containing sample core and remove barrel.
- Insert the syringe plunger and carefully extrude the equal portions representing Top, middle, bottom of container.
- Perform assay separately for each portions

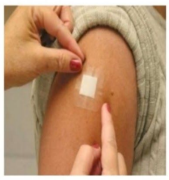


Test for rate of absorption

- The diadermatic ointment should be evaluated for the rate of absorption of drug into the blood stream.
- This test can be done in-vivo only.
- The ointment should be applied over a definite area of the skin by rubbing.
- At regular intervals of time, serum and urine samples should be analyzed for the quantity of drug absorbed. The rate of absorption i.e., the amount of drug absorbed per unit time should be more.

Test of Non-irritancy

- The bases used in the formulation of ointments may cause irritation or allergic reactions.
- Non-irritancy of the preparation is evaluated by patch test.
- In this test 24 human volunteers are selected.
- Daily the type of pharmacological action observed is noted. No visible reaction or erythema or intense erythema with edema and vesicular erosion should occur.
- A good ointment base shows no visible reaction.



Test of rate of penetration

- The difference between the initial and the final weights of the preparation gives the amount of preparation penetrated through the skin and this when divided by the area and time period of application gives the rate of penetration of the preparation. The test should be repeated twice or thrice. The rate of penetration of a semisolid dosage form is crucial in the onset and duration of action of the drug.
- Weighed quantity of the preparation should be applied over selected area of the skin for a definite period of time.
- Then the preparation left over is collected and weighed.