**Semisolid dosage form**

Ointments, creams, paste and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed on the surface of the eye, or used nasally, vaginally, or rectally. Most of these preparations are used for the effects of the therapeutic agents they contain. The un-medicated ones are used for their physical effects as protectants or lubricants. Topical preparations are used for both local and systemic effects.

**Pharmaceutical ointments and pastes**

**General description**

Pharmaceutical ointments are semisolid systems that are applied externally, primarily to the skin and also to mucous membranes, e.g. the rectum, the vagina/vulva, the eye. Typically, medicated ointments are used for the treatment of infection, inflammation and pruritus. However, non-medicated ointments are commonly used due to their emollient/lubricating properties. Pharmaceutical pastes are generally composed of ointment bases that contain a high concentration (frequently 50% w/w) of dispersed drug. The viscosity of pharmaceutical pastes is greater than that of pharmaceutical ointments.

**Advantages**

1. Pharmaceutical ointments may be easily spread on skin, being retained at the site of application as an occlusive layer, thereby preventing moisture loss from the skin. This is particularly useful whenever restoration of the physical characteristics of the skin is required (e.g. due to inflammation).

2. Pharmaceutical ointments are associated with lubricating properties, properties that may be employed to reduce trauma of an affected site upon spreading.

3. In general, pharmaceutical ointments persist at the site of application, enabling the duration of drug release to be greater than for many other topical dosage forms. The increased viscosity of pharmaceutical pastes ensures that a thick film of the dosage form is applied to the site of action, which shows excellent persistence. This
property is particularly useful if protection of an inflamed site is required, e.g. in eczema, psoriasis.

4. The hydrophobicity and retention of pharmaceutical ointments are useful attributes whenever applied to mucosa, e.g. inflamed haemorrhoids, eyelids, where fluid flow/inflammation at these sites would normally serve to remove other formulations (e.g. oil in water creams) by dilution. It should be noted, however, that spreading of ointments on to moist surfaces may be difficult due to the hydrophobic properties of most ointments.

**Disadvantages**

1. Pharmaceutical ointments are generally greasy and difficult to remove (and are therefore often cosmetically unacceptable). Similarly, liniments and lotions may also be cosmetically unacceptable to the patient and difficult to use.

2. Pharmaceutical pastes are generally applied as a thick layer at the required site and are therefore considered to be cosmetically unacceptable.

3. Staining of clothes is often associated with the use of pharmaceutical pastes and ointments.

4. The viscosity of pharmaceutical ointments, and in particular pastes, may be problematic in ensuring spreading of the dosage form over the affected site. Conversely, the low viscosity of liniments and lotions may result in application difficulties.

5. Pharmaceutical ointments may not be applied to exuding sites however, please note that this does not hold for pastes. Liniments may not be applied to broken skin.
6. Problems concerning drug release from pharmaceutical ointments may occur if the drug has limited solubility in the ointment base.

7. Pharmaceutical pastes are generally not applied to the hair due to difficulties associated with removal.

8. Therapeutic agents that are prone to hydrolysis should not be formulated into aqueous gels.

**Introduction**

The formulation of ointments and pastes involves the dispersal or dissolution of the selected therapeutic agent into an ointment base and, therefore, in addition to the physical properties of the dispersed/dissolved drug, the physicochemical properties of the ointment base are fundamental to the clinical and non-clinical performance of this type of dosage form. The choice of ointment base is dependent on several factors, including: (1) the site of application; (2) the required rate of drug release; (3) the chemical stability of the drug; and (4) the effect of the therapeutic agent on formulation viscosity.

**The site of application**

In certain clinical conditions the site to which the ointment will be applied may be dry, e.g. psoriasis, or moist. If the area is dry, ointments are often used to occlude the site, thereby retaining moisture. Indeed, this effect is considered to play an important role in the treatment of certain clinical conditions. Conversely, occlusive ointment bases are not applied to sites in which there is fluid exudate.

**The required rate of drug release**

Following application, the therapeutic agent must be released to exert its pharmacological effect, either locally or, after absorption, systemically. Drug release from the ointment base requires solubility of the therapeutic agent within the formulation. This will allow diffusion of the therapeutic agent (a molecular process) through the ointment base until it reaches the biological substrate. Therefore the choice of the ointment base is partially dictated by the physicochemical properties (and in particular the solubility) of the therapeutic agent.

**The chemical stability of the drug**

If a therapeutic agent is prone to hydrolysis, incorporation into a water-based formulation, e.g. oil in water creams, may lead to drug degradation.
and hence a shortened shelf-life. This problem may be obviated by incorporating the drug into a hydrophobic ointment base. For example, the shelf-life of hydrocortisone is markedly greater in an ointment formulation than in an oil in water cream formulation.

**The effect of the therapeutic agent on formulation viscosity**

The effect of the physical incorporation of a therapeutic agent into an ointment base on the rheological properties of the formulated product will be dependent on the required drug concentration, the physical properties of the therapeutic agent and the chemical composition and viscosity of the ointment base. Therefore, it is important that an ointment base is selected that will produce a product that may be readily applied to the required site. In light of the high drug content, this point is particularly important in the formulation of pastes.

**Types of base for ointments and pastes**

There are four types of base that are used to formulate pharmaceutical ointments and pastes: (1) hydrocarbon; (2) absorption; (3) water-miscible/removable; and (4) water-soluble.

**Hydrocarbon bases**

Hydrocarbon bases are non-aqueous formulations, based on various paraffins, that have the following properties:

- emollient, thereby restricting water loss from the site of application due to the formation of an occlusive film
- excellent retention on the skin
- predominantly hydrophobic, and therefore difficult to remove from the skin by washing and difficult to apply to (spread over) wet surfaces (e.g. mucous membranes, wet skin)
- only a low concentration (5%) of water may be incorporated into hydrocarbon bases (with careful mixing)
- chemically inert.

Hydrocarbon bases frequently contain the following components: (1) hard paraffin; (2) white/yellow soft paraffin; (3) liquid paraffin (mineral oil); and (4) microcrystalline wax.
1-Hard paraffin

This is a mixture of solid saturated hydrocarbons that are derived from petroleum. Hard paraffin is a colourless or white wax-like material that is physically composed of a mixture of microcrystals. The melting temperature of hard paraffin is between 47 and 65°C and, when solid, it is used to enhance the rheological properties of ointment bases.

2-White/yellow soft paraffin

This is a purified mixture of semisolid hydrocarbons (containing branched, linear and cyclic chains) that are derived from petroleum. White/yellow soft paraffin consists of microcrystals embedded in a gel composed of liquid and amorphous hydrocarbons. The melting range of the soft paraffins is between 38 and 60°C. White soft paraffin and yellow soft paraffin may be used as an ointment base without the need for additional components, although it may be combined with liquid paraffin.

3-Liquid paraffin (mineral oil)

This is a mixture of saturated aliphatic (C14–C18) and cyclic hydrocarbons that have been refined from petroleum. It is usually
formulated with white/yellow soft paraffin to achieve the required viscosity for application to the required site. Formulations containing liquid paraffin require the incorporation of an antioxidant due to the ability of this material to undergo oxidation.

4-Microcrystalline wax

This is a solid mixture of saturated alkanes (both linear and branched) with a defined range of carbon chain lengths (C41–C57). This excipient is used to enhance the viscosity of ointments (and creams). One of the advantages of microcrystalline wax is the greater physical stability provided to formulations containing liquid paraffin (reduced bleeding of the liquid component).

Absorption bases

Unlike hydrocarbon bases, absorption bases may be formulated to contain significant amounts of an aqueous phase. These may be either non-aqueous formulations to which an aqueous phase may be added to produce a water in oil emulsion (termed nonemulsified bases) or water in oil emulsions that can facilitate the incorporation of an aqueous phase (without phase inversion or cracking). Although absorption bases can accommodate a larger volume of aqueous phase than hydrophobic bases, they are still difficult to remove from the site of application by washing. This is due to the predominantly hydrophobic properties of this formulation class.

1. Non-emulsified bases

These are hydrophobic formulations to which water may be added. Following application, a film is formed that offers occlusion (and hence
emollient properties); however, the extent of occlusion is less than for hydrocarbon bases. The spreading properties of these formulations are more favourable than for hydrocarbon bases. Typically non-emulsified bases are commonly composed of: (1) one or more paraffins (2) a sterol-based emulsifying agent. Examples of the types of emulsifying agents used in absorption bases include: (1) lanolin (wool fat); (2) lanolin alcohols (wool alcohols); and (3) beeswax (white or yellow).

2. Water in oil emulsions

Ointment bases in this category can accommodate a greater concentration of water but yet can still provide similar performance to that provided by non-emulsified bases with respect to, e.g. occlusion, spreading properties. A common excipient that is employed in the formulation of this type of ointment base is hydrous lanolin, which is a mixture of lanolin and 25–30% water. It is incorporated into paraffins and oils to produce a base that can incorporate the subsequent addition of an aqueous phase. The water content of bases that have been formulated using hydrous lanolin is significant, e.g. Oily Cream BP is a water in oil emulsion ointment base that is composed of wool alcohols (50% w/w) and water (50% w/w).

Water-miscible/removable bases

These are water-miscible bases that are used to form oil in water emulsions for topical applications. The use of these bases offers a number of advantages, including:

- They are able to accommodate large volumes of water, e.g. aqueous solutions of drug, excess moisture at the site of application, e.g. exudate from abrasions and wounds.
- They are not occlusive.
- They may be easily washed from the skin and from clothing. Furthermore, they may be readily applied to (and removed from) hair.
- They are aesthetically pleasing.

The BP describes three water-miscible/removable bases:

1. emulsifying ointment
2. cetrimide emulsifying ointment
3. cetomacrogol emulsifying ointment.
Each of these contains:

- liquid paraffin 20% w/w
- white soft paraffin 50% w/w
- anionic, cationic or non-ionic emulsifying wax 30% w/w.

As may be observed, an important component of this ointment base is emulsifying wax, of which there are three types: (1) anionic; (2) non-ionic; and (3) cationic. The important properties of these waxes are as follows:

**Anionic emulsifying wax**

- This is a waxy solid that, when incorporated into a paraffin base, may be used to produce an oil in water emulsion, e.g. Aqueous Cream BP (which contains 10% w/w anionic emulsifying wax).
- Anionic emulsifying wax is composed of:
  1. cetostearyl alcohol 90 g
  2. sodium lauryl sulphate 10 g
  3. purified water 4 ml.

**Non-ionic emulsifying wax**

- This is also referred to as Cetomacrogol Emulsifying Wax BP and is composed of:
  1. cetostearyl alcohol 800 g
  2. cetomacrogol 1000 (macrogol cetostearyl ether 22) 200 g.

**Cationic emulsifying wax**

- This is also referred to as Cetrimide Emulsifying Wax BP.
- Cationic Emulsifying Wax BP is composed of:
  1. Cetostearyl alcohol 900 g
  2. cetrimide 100 g.

**Water-soluble bases**

Water-soluble bases are composed entirely of water-soluble ingredients. The advantages of the use of these bases include:

- They are non-greasy and may be easily removed by washing.
- They are miscible with exudates from inflamed sites.
- They are generally compatible with the vast majority of therapeutic agents.
Water-soluble bases are predominantly prepared using mixtures of different molecular weights of polyethylene glycol to produce the required ointment consistency. Lower average molecular weights of this polymer (200, 400 and 600 g/mol) are liquids. As the average molecular weight increases, the consistency of this polymer changes from a liquid to a waxy solid (1000 g/mol).

Blends of 60% w/w polyethylene glycol 400 (a liquid) and 40% w/w polyethylene glycol 4000 (a solid) have been used as a water-soluble ointment base. If required, the consistency may be increased by lowering the ratio of polyethylene glycol 400 to polyethylene glycol 4000 in the ointment base. Blending the two polyethylene glycol fractions is performed by heating the mixture followed by cooling of the homogeneous liquid at a controlled rate. The main disadvantage associated with water-soluble bases is their inability to incorporate large volumes of aqueous solutions as these will soften and, if the concentration of water is large enough (5% w/w), dissolve the ointment base. Therefore the use of these bases is usually reserved for the incorporation of solid therapeutic agents. However, these bases may incorporate up to 25% of an aqueous solution if a portion of the lower-molecular-weight polyethylene glycol is replaced with stearyl alcohol. This will enhance the mechanical properties of the ointment.

Selection of the Appropriate Base

Selection of the base to use in the formulation of an ointment depends on careful assessment of a number of factors, including the following:

1. Desired release rate of the drug substance from the ointment base
2. Desirability of topical or percutaneous drug absorption
3. Desirability of occlusion of moisture from the Stability of the drug in the ointment base
4. Effect, if any, of the drug on the consistency or other features of the ointment base
5. Desire for a base easily removed by washing with water
6. Characteristics of the surface to which it is applied For example, an ointment is generally applied to dry, scaly skin; a cream is applied to weeping or oozing surfaces; and a lotion is applied to intertriginous areas or where friction may
occur, as between the thighs or under the armpit. The base that provides the best combination of the most desired attributes should be selected.

**Miscellaneous excipients used in the formulation of ointments and pastes**

The therapeutic agent may be directly incorporated as a solid component or, in the case of the absorption and water-miscible bases, the addition may be in the form of a solution. This solution may be aqueous, alcoholic e.g. propylene glycol, glycerol, or hydroalcoholic and must not adversely affect the physical stability and/or appearance of the formulated product. Other excipients may be included in ointments and pastes, including: (1) additional/alternative solvents; (2) preservatives; and (3) antioxidant

**Additional/alternative solvents**

These are hydrophobic liquid components that may be added to ointment bases (predominantly hydrophobic or absorption bases). Examples of these include: (1) liquid silicone; (2) vegetable oils; and (3) organic esters.

**Liquid silicone**

This may be used in barrier ointments due to the water-repellent properties of this component.

**Vegetable oils**

Vegetable oils may be used either to replace mineral oils or, alternatively, may be added to hydrophobic or absorption bases to increase the emollient properties of the formulated product. Examples of oils that are used for this purpose are coconut oil and arachis oil.

**Organic esters**

These may be used partly to replace a mineral oil to enhance the spreadability and to enhance drug dissolution within the ointment base. One of the most commonly used examples is isopropyl myristate.

**Preservatives**

Topically applied ointments and pastes are not sterile products; however, they are manufactured under clean conditions to minimise the
microbial bioburden within the formulated product. Ointments/pastes that do not contain water do not usually require the addition of a preservative (due to the low water activity in the formulation). However if the product contains water, then a preservative will be required. Preservatives that may be used in formulations designed for external use include:

1. phenolics: phenol (0.2–0.5%), chlorocresol (0.075–0.12%)
2. benzoic acid and salts (0.1–0.3%)
3. methylparabens (methylparahydroxybenzoic acid)(0.02–0.3%)
4. propylparabens (methylparahydroxybenzoic acid) (0.02–0.3%)
5. benzyl alcohol (_3.0%)
6. phenoxyethanol (0.5–1.0%)

In the preservation of ointments, the same physicochemical and microbiological principles exist and therefore partitioning of the preservative from the aqueous to the non-aqueous phase may occur. Under these circumstances it is important to ensure that the required concentration (minimum inhibitory concentration) of the antimicrobial species is present within the aqueous phase.

**Antioxidants**

In pharmaceutical ointments antioxidants are employed to prevent or reduce oxidation of either the non-aqueous components of the ointment base (e.g. mineral/vegetable oils) and/or the therapeutic agent. The types of preservatives used for this purpose include:

1. lipophilic antioxidants (to be dissolved within the non-aqueous vehicle), e.g. butylated hydroxyanisole (0.005–0.02%), butylated hydroxytoluene (0.007–0.1%), propyl gallate (_1%)
2. hydrophilic antioxidants (to be dissolved in the aqueous phase), e.g. sodium metabisulphate (0.01–0.1%), sodium sulphite (0.1%).

**Manufacture of ointments and pastes**

The manufacture of ointments and pastes is similar to that described for emulsions and creams. The most straightforward example involves the dispersal of the powdered therapeutic agent into the preheated hydrocarbon base using a mechanical mixer. Heat is required to lower the viscosity of the base, thereby facilitating the mixing of the solid drug. If the therapeutic agent is incorporated into the ointment base as a separate liquid phase, the hydrophobic components and hydrophilic components
are separately dissolved in the lipophilic and hydrophilic liquid phases, respectively (again with the aid of heating and mechanical mixing). In general (following dissolution of the various components), the two phases are maintained at 70°C and then mixed together (with stirring).

Following complete mixing, the temperature of the formulation is gradually reduced to room temperature.

**Compendial Requirements for Ointments**

Ointments and other semisolid dosage forms must meet USP tests for **microbial content, minimum fill, packaging, storage, and labeling.** Ophthalmic ointments must also meet tests for **sterility and metal particles** content.

**Microbial Content**

With the exception of ophthalmic preparations, topical applications are not required to be sterile. They must, however, meet acceptable standards.
for microbial content, and preparations prone to microbial growth must contain antimicrobial preservatives. Microbial limits are stated for certain articles in the USP. For example, Betamethasone Valerate Ointment, USP, must meet the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa. These particular microbes have special importance in dermatologic preparations because of their capacity to infect the skin, which for patients being treated for a skin condition, is already compromised.

**PASTES**

Pastes maybe defined as ointments incorporating a high percentage of insoluble particulate solids, sometimes as much as or more than 50%. The use of this high amount of insoluble particulate matter renders a stiffness to the system as a result of direct interactions between the dispersed particulates and by absorption of the liquid hydrocarbons from the vehicles onto the surface of the particles. Because of the stiffness, they remain in place after application and are used effectively to absorb serous secretions. Pastes as such are not suited for application to hairy parts of the body. Examples of insoluble ingredients serving as the dispersed phase include starch, zinc oxide, and calcium carbonate. Pastes make good protective barriers for the following reasons. In addition to forming an unbroken film, pastes also absorb and neutralize certain harmful chemicals before they reach the skin surface. This last feature is attributed to the presence of insoluble particulate matter within the paste formulations. For example, for the treatment of diaper rash, when spread over the baby’s bottom, the pastes absorb irritants formed by bacterial action on urine.

Pastes also provide a protective layer over skin lesions and, when covered with suitable dressings, prevent excoriation of the patient’s skin by scratching. Pastes afford emollient action as do ointments. In addition, the water-impermeable film formed on application is opaque and thus can often serve as a sunblock. Pastes are less greasy than ointments because of the absorption of the fluid hydrocarbon fraction to the insoluble particles.

A clinically distinctive feature, which is generally attributed to pastes, is the ability to absorb exudates by nature of the powder or other absorptive components.
GELS

Gels are defined as semisolid preparations consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly-like through the addition of a gelling agent. Gels are an intermediate state of matter, containing both solid and liquid components. The solid component comprises a three-dimensional network of interconnected molecules or aggregates that immobilize the liquid in the continuous phase. Gels may be classified into two primary types: hydrogels, which have an aqueous continuous phase, and organogels, which have an organic solvent as the liquid continuous medium. Gels may also be classified based on the nature of the bonds involved in the three-dimensional solid network: chemical gels form when strong covalent bonds hold the network together, and physical gels form when hydrogen bonds and electrostatic and van der Waals interactions maintain the gel network. Gelling agents commonly used are synthetic macromolecules (e.g., carbomer 934), cellulose derivatives (e.g., carboxymethylcellulose and hydroxypropylmethylcellulose), and natural gums (e.g., tragacanth).

Gels may be classified as two-phase or single-phase systems. A two-phase gel system consists of flocules of small distinct particles rather than large molecules, thus called a two-phase system often referred to as a magma. Milk of magnesia (or magnesia magma), which comprises a gelatinous precipitate of magnesium hydroxide, is an example of such a system.

A typical gel formulation may contain, apart from the gelling agent and water, a drug substance, cosolvents such as alcohol and/or propylene glycol, antimicrobial preservatives such as methylparaben and propylparaben or chlorhexidine gluconate, and stabilizers such as edetate disodium. Medicated gels may be prepared for administration by various routes including topically to the skin or eye, nasally, vaginally, and rectally.